PRESCRIPTION ANALGESIC USE AND MISUSE AMONG PEOPLE LIVING WITH HIV IN THE UNITED STATES

by
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Abstract

Background Opioid misuse is a growing public health issue in the United States and is particularly concerning among people living with HIV (PLWH). Though PLWH are at high risk for opioid misuse, little research is available to describe or quantify risk factors for their elevated risk. Describing the trends in opioid prescribing among PLWH and identifying characteristics of PLWH at highest risk for opioid misuse can help to guide the treatment of chronic pain while minimizing potential harms.

Methods We examined trends in opioid and non-opioid oral analgesic prescribing among PLWH compared to individuals without HIV. Next, we identified factors associated with high-risk opioid use by analyzing prescription claims from individuals attending HIV clinics in the United States. Finally, we applied an indirect questioning technique to estimate the prevalence of opioid diversion in the absence of social desirability bias.

Results We found an increasing trend in prevalence for both opioid and non-opioid analgesics between 2001-2009 regardless of HIV status. In all years, PLWH received more analgesic prescriptions compared to individuals without HIV. PLWH had a higher incidence of chronic opioid therapy (COT), defined as ≥90 consecutive days of opioid use, but the increased hazard for COT was explained by differences in co-morbidities. High-risk opioid use was common among PLWH, with approximately one third of PLWH who had received an opioid prescription meeting high-risk use criteria. Nearly half of all high-risk opioid use occurred within one year of receiving an opioid prescription. Using an indirect questioning technique, we found that 11.5% of patients at an urban HIV clinic had ever given away or sold their opioid prescriptions. This prevalence of opioid diversion was twice as high as the prevalence obtained by directly asking patients if they had ever diverted opioids.

Conclusion High rates of opioid prescribing and COT among PLWH are concerning because they may lead to opioid misuse; high-risk use patterns and opioid diversion were both common in our study. Applying our results to assess patients' risk for opioid misuse and carefully monitoring prescribing patterns to avoid over-prescribing may help to mitigate adverse consequences of opioid misuse and reduce opioid diversion.

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Chapter 1: Introduction

Background

Chronic pain represents a serious healthcare burden in the United States, leading to a movement to measure pain as the fifth vital sign in many medical facilities[1]. This practice began informally in the mid-1990s and was officially adopted by the Joint Commission on Accreditation of Healthcare Organizations in 1999[2]. A variety of treatments for pain exist, including physical therapy, psychological approaches such as meditation or cognitive behavioral therapy, and pharmaceuticals[3]. Pharmaceutical pain medication serves as a widely used treatment for pain and is the subject of much research and debate due to the increasing occurrence of misuse of the drugs[4–6]. The experience of pain and associated treatment options are of particular concern among people living with HIV (PLWH), as this population has a higher prevalence of risk factors both for developing pain and for misusing prescription pain medications.

Pharmaceutical pain treatment

Pharmaceuticals have become a common treatment for patients with pain, with over 200 million claims for opioid analgesics being dispensed in the United States in 2000[7]. Analgesics, the broad class of drugs used to treat pain, include non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, anticonvulsants, NMDA agonists, and opioids[8]. While all analgesics cause side effects, opioids are particularly dangerous because of their addictive nature. In addition to more general side effects such as sedation, dizziness, nausea, vomiting, and constipation, opioids can cause physical dependence, tolerance, and addiction[9]. Because of the ability of opioids to cause dependency, controversy exists as to whether they should be used for the treatment of long-term chronic pain[9], and medical providers must use caution when prescribing the drugs to patients with a tendency towards misuse.

Despite the controversy, rates of opioid prescribing have increased dramatically over the past two decades. The number of opioid prescriptions dispensed in the United States increased annually since the turn of the century, reaching a peak of 81.3 prescriptions per 100 Americans in 2012[10]. Prescribing guidelines that focus on reducing inappropriate opioid prescribing and the development of interventions such as prescription drug monitoring programs have helped to halt the increase in opioid dispensing, leading to a slight decline in opioid prescribing since 2013[11]. Nonetheless, we are still in the midst of a serious opioid epidemic as deaths from overdose and the prevalence of opioid misuse continue to rise[12].

As of 2011, drug poisonings surpassed motor vehicle accidents as the leading cause of injury death in the United States, with a majority of the poisonings attributed to opioids[13]. Approximately half of opioid overdose deaths involve a prescription opioid, with more than 15,000 deaths involving a prescription opioid in 2015[14]. Another 2 million Americans suffer from substance use disorders related to prescription opioids[15]. With appropriate interventions, the morbidity and mortality associated with prescription opioid use can be prevented.

Chronic pain and opioid treatment among PLWH

Among PLWH, chronic pain is highly prevalent, with a prevalence estimates ranging from 25% to 80% among PLWH[16] and estimates ranging from 61% to 80% among individuals with AIDS[17]. Common types of pain reported among PLWH include HIV-related headaches, peripheral neuropathy, and back pain[18]. The increased pain experienced by PLWH compared to HIV-uninfected individuals is also due in part to HIV-associated neuropathy and ART-toxic neuropathy[19]. Improvements to combination antiretroviral therapy have led to a decreasing prevalence of symptomatic peripheral neuropathy[20], but reports of increased levels of pain among PLWH still persist[21]. Pain often co-exists depressive symptoms and anxiety; higher rates of mental health co-morbidities among PLWH may contribute to their continued increase in chronic pain compared to the general population[21].

The use of opioids to ameliorate pain has been a controversial topic for all patients, and is particularly controversial among populations with a history of drug abuse. PLWH have a higher prevalence of both substance abuse and mental health disorders compared to the general population, both of which are risk factors of opioid misuse; as such, PLWH are at high-risk for developing aberrant opioid use[19]. This poses a challenge to clinicians treating pain among PLWH, as there must be a careful balance between treating symptoms and instigating a tendency towards drug abuse.

Likely because of the high-risk characteristics exhibited by PLWH, there have been reports of under-treatment of pain among PLWH since 1997[22–24]. Differences in the prevalence of pain by HIV status make it difficult to assess this claim, but research suggests that PLWH may in fact receive more opioid prescriptions compared to the general population[25,26]. Additionally, opioid misuse is more common among PLWH compared to individuals without HIV[21,27], indicating that appropriate prescribing and careful monitoring of opioid therapy is especially important in this population.

Opioid diversion

Consequences of opioid misuse not only lead to abuse and dependence, but also diversion, which is the unlawful transfer of prescribed opioids. Opioid diversion is particularly dangerous, as it results in unmonitored consumption of the drugs. The National Survey on Drug Use and Health found that over 70% of individuals who abuse prescription painkillers received the drugs through diversion[28]. Despite the high prevalence and severe negative consequences of opioid diversion, efforts to combat diversion in the United States are inconsistent and largely ineffective[28], leading to a continued problem with opioid diversion across the country.

Data on the prevalence of opioid diversion are very limited, due in part to challenges associated with measuring sensitive behaviors: individuals are hesitant to self-report behaviors such as opioid overuse or diversion that are stigmatized or illegal. The few studies that have examined opioid diversion have been primarily in high-risk European populations and have estimated the prevalence of opioid diversion between 10-34% among patients in opioid substitution treatment programs[29,30]. Though we are not aware of a study designed to estimate the prevalence of opioid diversion among PLWH specifically, two studies that examined the use of street methadone and buprenorphine among injection drug users in Baltimore, MD found no association between HIV status and the prevalence of street methadone or buprenorphine use[31,32]. Further research is needed to quantify the prevalence of opioid diversion among PLWH, as this estimate is currently unknown.

An indirect method for estimating the prevalence of opioid misuse may provide a more accurate measurement and can be used to validate direct estimation methods. With an indirect questioning method, researchers induce a known amount of measurement error into the study design, which provides anonymity to the respondent and increases the likelihood of honest responses. Under the assumptions that the induced measurement error is known and that the respondents understood the questioning method and answered correctly, researchers can obtain accurate estimates for the prevalence of the sensitive behavior by adjusting for the induced measurement error.

Indirect questioning methods

Indirect questioning methods were first introduced in 1965 when Warner published a paper on randomized response to eliminate "evasive answer bias"[33]. Under the Warner method, a respondent is presented with a spinner with two true/false questions, where question A is the complement to question B. The respondent spins the spinner, unobserved by the interviewer, and answers the question to which the spinner points. This method elicits more honest responses than direct questioning because the interviewer does not know which question the respondent is answering. However, drawbacks include the necessity for all respondents to answer a sensitive question and the infeasibility of a non face-to-face questionnaire because of the need for a randomization device.

To avoid requiring all respondents to answer a sensitive question, the unrelated question model, developed in 1967, randomly assigns respondents to answer either the sensitive question or an unrelated question[34]. Similarly, under the forced choice randomized response technique developed in 1971, respondents are randomized to answer either "yes", "no", or the truth[35]. However, these modifications to Warner's randomized response technique include a self-protective "no" answer that may reduce the accuracy of responses and, like the Warner method, require a randomization device.

As an alternative to the randomized response techniques, the item count technique, or unmatched count technique[36], presents two groups of respondents each with a list of true/false questions and asks the respondents to report the number of true responses in the list. One list contains the sensitive question of interest; the second list does not. Under the assumption that the prevalence of the sensitive question is the same between the two groups, the difference in the number of true responses between the two groups provides an estimate for the prevalence of the sensitive question. The item count technique does not have a self-protective "no" answer and can be completed using mail-in questionnaire; however, prevalence estimates under this method have a large variance, requiring a large sample size for precision.

More recently, the crosswise method was developed by Yu et al.[37] as another non-randomized response method for indirect questioning. Under this method, respondents simultaneously answer two true/false questions (one sensitive question and one non-sensitive question) by stating whether the answer to both questions is the same or different. Because the respondent does not state whether the responses are true or false, the stigma associated with answering the sensitive question decreases and the respondent is more likely to provide an honest answer. In empirical testing, the crosswise method was shown to reduce under-reporting due to social desirability bias as compared to direct questioning[38]; however, few applications of this method exist in the literature.

Gaps in Knowledge

Trends in oral analgesic prescriptions have been examined in the general population and have shown an increase in opioid prescriptions, but not non-opioid analgesic prescriptions, over the past decade[39]. However, similar research has not been conducted specifically within an HIV-infected population. Because PLWH are at a high risk for opioid misuse, prescribing patterns may differ between HIV-infected and uninfected individuals despite similar symptoms and reports of pain. Examining trends in the receipt of oral analgesics can help describe the setting in which PLWH are being treated for pain and can provide evidence for the presence or absence of differential pain treatment among patients by HIV status. Identifying and quantifying differential treatment patterns can help to guide appropriate treatment recommendations for managing pain in PLWH.

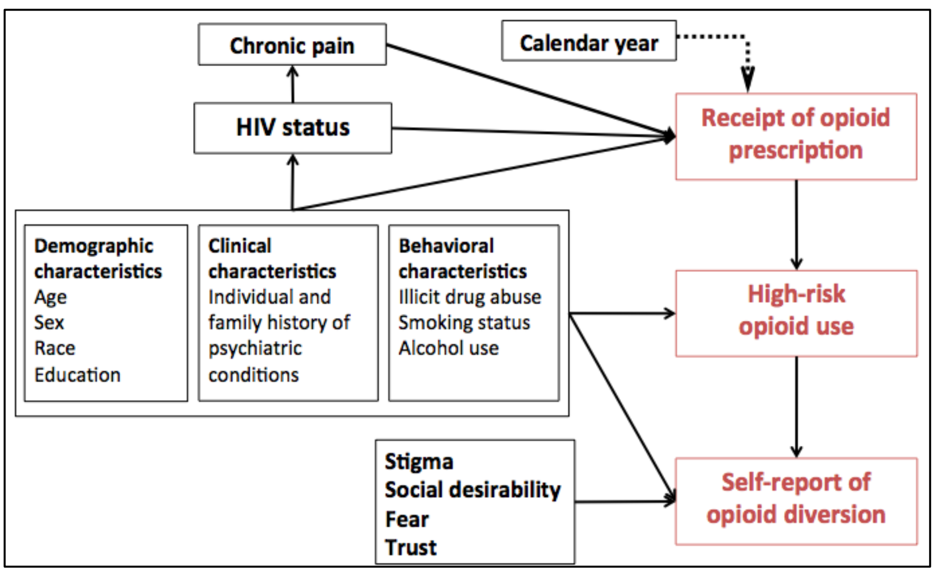
There is a small body of literature describing predictors of aberrant opioid use among PLWH[19,21,40,27], however, these studies have been cross-sectional in nature and were unable to describe the time from initiation of opioid therapy to the development of opioid misuse. Further research that describes predictors of high-risk use among PLWH and characteristics associated with a faster progression to high-risk use can be used to better target resources to prevent or mitigate opioid misuse. Supplementing the current body of literature on predictors of high-risk opioid use can also guide future studies into examining causal relationships between modifiable risk factors and high-risk opioid use, with the ultimate goal of reducing opioid-related morbidity and mortality.

Assessing risk factors or predictors for opioid diversion has proven challenging. Clinical cohort studies face difficulties in assessing opioid diversion, as self-report is associated with questionable reliability and toxicology screens can be costly. Studies that use prescription claims to identify opioid misuse cannot identify diversion, as claims do not indicate whether the individual to whom the drug was prescribed has taken it as intended. Improved methodological techniques to better estimate the prevalence and risk factors for opioid diversion can help to describe the scope of the opioid diversion problem and may aid in developing recommendations for appropriate prescribing behaviors. Because a majority of opioid misuse occurs among patients who received the drugs illegally, directly targeting opioid diversion as a key element of the opioid epidemic that requires intervention can have a huge impact on reducing the burden of the problem.

Conceptual Framework

The framework depicted in Figure 1 describes the conceptual model underlying this research. In this framework, we describe the associations we hypothesize exist between receiving an opioid analgesic prescription and developing high-risk opioid use.

Figure 1: Conceptual Framework



We expect that having HIV-infection will lead to a decrease in oral analgesic prescriptions, despite a similar or increased level of pain reported by the individuals. Further, we hypothesize that age, sex, race, presence of psychiatric illness, and history of illicit substance use will be associated with both the prescription of an oral analgesic and the development of high-risk use. Additionally, we expect that the patterns of prescription drug use will change over time, as indicated by the calendar year box that suggests a modification of the exposure-outcome by time. Finally, we believe similar demographic, clinical, and behavioral characteristics that are related to high-risk opioid use will be associated with self-reported opioid diversion, which is also impacted by stigma, social desirability, fear, and trust.

Specific Aims

PLWH are at an increased risk for pain, both due to HIV-associated neuropathy and to ART-toxic neuropathy. Treatment for such pain commonly involves the use of prescription pharmaceuticals, including opioid analgesics. Because PLWH engage in high-risk behaviors at a higher rate than their uninfected counterparts, they are also at increased risk for misusing opioid prescriptions and consequently may receive opioid prescriptions less readily than lower-risk individuals. This research aims to compare trends in analgesic use among PLWH and individuals without HIV, to determine risk factors associated with high-risk opioid use among PLWH, and to estimate the prevalence of opioid diversion among PLWH in Baltimore, MD.

Aim 1: To compare trends in the receipt of opioid and non-opioid analgesics among PLWH versus HIV-uninfected individuals over time and to estimate the incidence of progression to chronic opioid therapy among opioid-naïve PLWH.

Several studies have reported an under-treatment of pain among PLWH. Therefore, we aim to compare the prescribing patterns of oral analgesics between PLWH and HIV-uninfected individuals and to determine whether PLWH have a higher incidence of progression to chronic opioid use.

Hypothesis 1**:** The increase in the prevalence of opioid prescriptions over time will be greater among HIV-uninfected individuals compared to PLWH.

Hypothesis 2: PLWH will have a higher incidence of progression to chronic opioid therapy compared to individuals without HIV.

Aim 2: To identify risk factors for high-risk opioid use and time to high-risk use among PLWH who receive a prescription for opioids.

Among HIV-uninfected individuals, psychiatric illness and a history of substance abuse have been found to predict opioid misuse, but this association has not been replicated among PLWH.

Hypothesis**:** PLWH with a diagnosis of psychiatric illness and with a history of drug abuse will have an increased prevalence of high-risk opioid use and will have a shorter time to high-risk use compared to individuals without these diagnoses.

Aim 3: To describe the prevalence of opioid diversion among PLWH as determined by indirect questioning and to characterize risk factors for diversion.

Accurately measuring the prevalence of opioid misuse presents challenges, as individuals are often hesitant to respond accurately to sensitive questions. Indirect questioning techniques can help to overcome this challenge and can enable the evaluation of factors associated with opioid diversion.

Hypothesis**:** The calculated prevalence of opioid diversion will be higher using indirect questioning compared to the prevalence calculated using direct questioning.

Overall Approach

The goals of this dissertation are to identify trends in the receipt of opioid and non-opioid analgesics over time by HIV status, to estimate the incidence of high-risk opioid use patterns, and to determine characteristics associated with PLWH who exhibit high-risk use behavior, including opioid diversion. The study populations include: 1) United States Medicaid enrollees, whose claims files contain medical and pharmaceutical data from all billable healthcare encounters, 2) the HIV Research Network, a national multisite longitudinal research study composed of 18 sites across the United States and 3) the Johns Hopkins HIV Clinical Cohort (JHHCC), a prospective cohort assembled in 1989 that follows HIV infected individuals in Baltimore, MD from the onset of clinical care at the HIV clinic to death or loss to follow up. The three studies conducted as part of this research help to fill gaps in the literature surrounding the opioid epidemic among PLWH in the United States.

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Chapter 2: Trends in opioid and non-opioid prescription oral analgesics by HIV status

Abstract

Background. People living with HIV (PLWH) experience a higher prevalence of pain compared to their HIV-uninfected counterparts. Detailed, nationwide trends in the use of opioid and non-opioid analgesics among PLWH compared to individuals without HIV and the incidence of progression to chronic opioid therapy (COT) by HIV status are not well described.

Methods. We analyzed Medicaid pharmaceutical claims from adults age 18-65 from 14 US states between 2001-2009 to identify rates of opioid and non-opioid analgesic prescriptions over time. We compared trends in prescribing rates by HIV status. Then, to reduce heterogeneity between PLWH and people without HIV, we 1) standardized the study sample to the characteristics of PLWH using inverse probability weights and 2) restricted the sample to a select subgroup of patients who shared a common comorbidity. The subgroup was defined by the presence of a diabetes diagnosis, chosen because of its relatively high prevalence and association with chronic pain. We estimated the incidence of COT among opioid-naïve individuals and estimated the association between HIV status and progression to chronic opioid use.

Results. Rates of both opioid and non-opioid analgesic prescriptions increased between 2001-2009. PLWH received approximately twice the number of analgesic prescriptions

compared to individuals without HIV. COT was more common among PLWH, with an incidence rate of 29.1 per 1,000 person-years (PY) compared to 9.3 per 1,000 PY among individuals without HIV. In an unadjusted Cox proportional hazards model, PLWH had 3.06 (95% CI 2.76-3.39) times the hazard of COT compared to individuals without HIV. When applying inverse probability of HIV weights and restricting the sample to patients with diabetes, the rates of all analgesic prescriptions were approximately equal by HIV status and the unadjusted hazard ratio for COT decreased to 1.46 (95% CI 1.31-1.63). After adjusting the Cox proportional hazards model for age, sex, state of residence, comorbidity score, depression, bipolar disorder, and schizophrenia, the increased hazard for COT in the weighted subsample decreased to 1.26 (95% CI 0.97-1.63).

Conclusions. Between 2001-2009, PLWH received more analgesic prescriptions compared to individuals without HIV, yet these differences appear to be primarily due to differences in demographics and co-morbidities. Nevertheless, the rate of COT is relatively high; HIV providers must be vigilant when prescribing analgesia to PLWH.

Introduction

Chronic pain is highly prevalent among people living with HIV (PLWH), with prevalence estimates ranging from 25% to 80% among PLWH[1] and estimates ranging from 61% to 80% among individuals with AIDS[2]. In addition to common types of pain, including headaches, peripheral neuropathy, and back pain[3], PLWH also experience HIV-associated neuropathy and ART-toxic neuropathy[4]. The development of improved combination antiretroviral therapy has led to a decreasing prevalence of symptomatic peripheral neuropathy[5], but HIV-infected individuals continue to report an increased level of pain compared to their uninfected counterparts[6]. Because pain is a complex multidimensional construct influenced by both physiological and psychological factors, high rates of psychological symptoms among PLWH may contribute to their higher prevalence of pain[6].

In the era of heightened concern over opioid misuse[7–10], treatment for chronic pain has become a great challenge. Because of the ability of opioids to cause dependency, controversy exists as to whether they should be used for the treatment of long-term chronic pain[7]; nonetheless, pharmaceuticals have become a common treatment for pain, with over 200 million claims for opioid analgesics being dispensed in the United States in 2000[11]. Reducing the number of opioid prescriptions in circulation and ensuring appropriate prescribing may help to minimize the consequences of the drug, particularly among populations at high risk for drug abuse.

PLWH are an especially vulnerable population with respect to opioid use. Not only do they experience a higher prevalence of pain, but they also have a high prevalence of drug abuse and psychological co-morbidities compared to the general population and are considered at high-risk for developing aberrant opioid use[4]. Likely because of the high risk characteristics exhibited by PLWH, there have been reports of under-treatment of pain among individuals living with HIV since 1997[12–14]. Nonetheless, recent studies have found an increased prevalence of opioid prescribing among PLWH compared to the general population[15,16]. However, these studies do not discuss trends in non-opioid analgesic prescriptions among PLWH and do not describe progression to incident chronic opioid use.

In this study, we compared trends in the prescription of both opioid and non-opioid analgesics among PLWH and individuals without HIV between 2001-2009. We looked at variations within these trends across age, sex, and state of residence. We then estimated the incidence of the development of chronic opioid therapy (COT), defined as ≥90 consecutive days with an opioid prescription, among opioid-naïve individuals and determined the association between HIV and COT.

Methods

Study sample

Data for this aim came from the Center for Medicare and Medicaid Services (CMS) Medicaid Analytic eXtract (MAX) claims files. Medicaid claims databases contain data on pharmaceutical prescriptions dispensed, clinical diagnoses, and medical service utilization from all billable healthcare interactions. The pharmaceutical data include comprehensive information on medications prescribed to Medicaid-eligible individuals, regardless of the prescribing physician. Because individuals receiving opioid medications occasionally seek prescriptions from multiple providers, a single database that captured all prescriptions was optimal for this analysis. A further benefit of the Medicaid database was the large volume of patients represented (over 50 million enrollees nationally). Finally, a large proportion (approximately 40%[17]) of insured PLWH are covered under Medicaid, indicating that a Medicaid is a rich data source from which to glean information about healthcare utilization among PLWH.

We analyzed data from 2001 through 2009, as these years represent a time period with a dramatic rise in the prevalence of opioid prescriptions and opioid overdose[18], after which there has been a steady decline[19]. Additionally, several new guidelines and policy initiatives were developed during this time to address growing concerns about opioid use[20]. Therefore, we expected to observe interesting trends in the use of opioids during these years.

We identified opioid and non-opioid oral analgesic prescriptions using the National Drug Code (NDC) coding system. The NDC was developed by the Food and Drug Administration (FDA) as part of Drug Listing Act of 1972 and provides a unique 10-digit number to all drugs available for commercial distribution in the United States. Using pre-identified NDC codes (see Supplementary Table 1), we identified all pharmaceutical claims for opioid and non-opioid analgesics, along with the date prescribed and total days supplied, among our study sample from 2001-2009.

We obtained demographic characteristics of the study participants, including age, sex, and state of residence, from the enrollment record of the MAX files. We identified medical conditions using the Johns Hopkins ACG® System 11.1, which applies propriety algorithms to identify chronic diseases using inpatient medical claims, pharmaceutical claims, and enrollment files. The ACG® System uses 12-month claims data to assess, annually, individual chronic conditions and to assign overall risk scores to individuals. In this analysis, we used five chronic conditions identified through the ACG® System, each of which we hypothesized to be related to the receipt of prescription analgesics: HIV, diabetes, depression, schizophrenia, and bipolar disorder, and we used the categorical risk score, "major ADG count" as a summary measure for the individual's overall chronic disease burden.

The cohort analyzed in this study was originally assembled for the purpose of creating a comparison group for the North American AIDS Cohort Collaboration of Research and Design (NA-ACCORD) studies. Because we had access to these Medicaid files through NA-ACCORD, we chose to analyze this pre-assembled cohort. The sample included HIV-infected individuals between the ages of 18 and 65 years who were insured under Medicaid between 2001-2009 in one of 14 states: Alabama, California, Colorado, Florida, Georgia, Illinois, Massachusetts, Maryland, North Carolina, New York, Ohio, Pennsylvania, Texas, and Washington. The analytic cohort was assembled using a closed cohort of individuals who were enrolled in Medicaid on January 1, 2001. Individuals remained in the cohort for every month in which they were enrolled in Medicaid until December 31, 2009. Because the dataset comprised a closed cohort, data were not available on individuals who were new Medicaid enrollees after January 1, 2001.

We excluded individuals with secondary insurance from the analysis, as Medicaid claims files do not contain information on prescriptions covered by other insurance. This exclusion criterion applied to individuals who had supplemental private insurance and those who were dual-eligible for both Medicaid and Medicare. Also, patients with gaps in coverage were excluded from the analysis for all years following the gap. Finally, we excluded patients from Florida because data were unavailable for all patients from Florida after 2001. Supplementary Table 2 shows the population of Medicaid enrollees by state in the source population and Supplementary Table 3 shows the analytic sample size after the exclusion criteria were applied.

Statistical methods

We examined: 1) trends in opioid and non-opioid oral analgesic prescriptions over time and 2) the incidence of chronic opioid use comparing PLWH to individuals without HIV. The trends we examined included the standardized number of analgesic prescriptions per 100 individuals and the proportion of days covered by an opioid or non-opioid analgesic. All analyses were first conducted on the full analytic sample and then, to create a more homogenous study sample and consequently improve comparability between the HIV and non-HIV groups, we restricted the sample to a subset of patients with diabetes.

Prevalence of opioid and non-opioid analgesics

To explore trends in opioid and non-opioid prescription oral analgesics over time, we created plots to depict the standardized rate of opioid and non-opioid analgesic prescriptions per 100 people by HIV status. We present the standardized rates of analgesic prescriptions among the full analytic sample and also among the diabetic subset. Also, to further ensure comparability between the HIV and non-HIV groups, we applied two sets of weights. First, we weighted the population to standardize the sample to the distribution of the characteristics among the HIV-infected individuals using inverse probability of HIV weights, as follows: PLWH were assigned a weight of 1 and individuals without HIV were given a weight corresponding to their estimated odds of having HIV according to a logistic regression model where HIV was modeled as a function of age, sex, state of residence, and major ADG count[21]. Second we calculated and applied inverse probability of censoring weights (IPCW) to account for differential censoring by HIV status. We calculated the IPCW using a logistic regression model for Medicaid dis-enrollment as a function of year, age, sex, state of residence, major ADG count, and HIV status.

In a second series of plots, we created boxplots by HIV status for the proportion of days covered (PDC) by opioid and non-opioid analgesic prescriptions (separately) among patients with at least one prescription opioid or non-opioid analgesic, respectively. All PDC boxplots display trends among the weighted study population, weighted by both IPTW and IPCW. We calculated PDC using SAS arrays and credited overlapping days supply by shifting the start date of prescriptions that began before the prior prescription ended[22]. We then describe the trends in opioid analgesics in more detail by showing boxplots stratified by age at baseline (18 to <35; 35 to <45; 45 to <55; 55 to <65), sex, and state of residence. We were unable to assess PDC for the state of Ohio because the number of days supplied per prescription was unavailable. Because we restricted these plots to patients with at least one opioid (or non-opioid), we also report the number and proportion of individuals in each year that received an opioid (or non-opioid) prescription.

Incident chronic opioid therapy

We examined COT among opioid-naïve individuals. To create a subset of opioid-naïve individuals, we identified and excluded all patients who received at least one opioid prescription during the first year of follow-up, as they represent prevalent opioid users. By implementing a one-year washout period, we were able to restrict the analysis to opioid-naïve patients, thereby allowing us to assume that the first opioid prescription in the prescriptions claims records represents an incident opioid prescription. We weighted the population by the inverse probability of censoring weights to account for differential dropout by HIV status. We accounted for differences in comorbidities by HIV status using regression adjustment.

We examined the incidence of COT among a population of opioid-naïve individuals using a time-to-event analysis with a time origin defined as January 1, 2002. We defined COT using a standard definition of 90 continuous days with an opioid prescription[23]. Patients were followed until the first of: the 90th day of opioid therapy, loss of Medicaid coverage (due to a change in insurance status or death), or December 31, 2009.

We plotted the cumulative incidence of COT using a Kaplan-Meier estimator and assessed the proportionality of the hazard of COT with respect to HIV-status. We then fit Cox proportional hazards models to estimate the crude and adjusted associations between HIV-status and COT among the weighted sample and among a subset of the weighted sample with diabetes. To ease computational burden, we selected a 10% random sample of the study population for the COT analyses.

Results

The source population contained 15,856,135 individuals. After applying the exclusion criteria, the study population decreased to 4,561,139 individuals. Of these, 54,120 (1.19%) had a diagnosis of HIV in 2001 and 288,027 (6.31%) had a diagnosis of diabetes in 2001. The sample size of the source population and eligible populations are shown by state in Supplementary Tables 2 and 3.

Within our analytic sample, PLWH differed from individuals without HIV with respect to most of the characteristics we measured. Slightly more than half (53%) of PLWH were male, whereas only 27% of individuals without HIV were male. PLWH were older, with a median age of 42 (IQR 37-38), compared to a median age of 34 (IQR 25-45) among individuals without HIV. Regarding state of residence, the highest proportion of PLWH was from New York (44%), whereas the most represented state among individuals without HIV was California (37%). Approximately 42% of PLWH were prevalent opioid users in 2001, compared to only 24% of individuals without HIV. Finally, diabetes, depression, bipolar disorder, and schizophrenia, were all more common among PLWH, with prevalence rates of 8%, 39%, 1%, and 3%, respectively, compared to prevalence rates of 6%, 17%, 0.4%, and 1%. Table 1 describes characteristics of the study sample.

Prevalence of opioid and non-opioid analgesics

Opioid and non-opioid analgesic prescription rates by HIV status are shown in Figure 2 (opioids) and Figure 3 (non-opioids), where the left panel depicts the full sample and right panel is restricted to those with diabetes. The figures depict both unadjusted trends (dashed lines) and trends weighted by IPTW and IPCW (solid lines). In both panels, all analgesic prescriptions rise over time between 2001 and 2009.

In unadjusted trends, PLWH received approximately twice the number of opioid analgesics compared to patients without HIV (Figure 2). When we applied the weights, trends in the non-HIV group increased causing PLWH to receive only 50-65% more opioid prescriptions compared to similar patients without HIV. Trends were more comparable among the diabetic subset: among the unadjusted sample with diabetes, PLWH received 25-35% more opioid prescriptions compared to individuals without HIV. When we applied the weights, the difference by HIV status among diabetics decreased to about 13-15%.

The absolute number of non-opioid analgesic prescriptions was higher than that of opioid prescriptions, but the patterns were similar: prescriptions increased over time in all groups, and the prevalence among PLWH was higher compared to individuals without HIV

(Figure 3). In unadjusted trends, the full sample of PLWH received approximately twice the number of non-opioid analgesics compared to patients without HIV; in weighted trends PLWH received about 20-30% more non-opioid analgesics. The difference by HIV status was less pronounced when restricting the sample to patients with diabetes, where PLWH received between 15-25% more non-opioid analgesic prescriptions compared to their non-HIV infected counterparts in unadjusted trends. Among the weighted diabetic subset, the prevalence of non-opioid analgesics was similar by HIV status until 2004, at which point PLWH received approximately 10% more non-opioid analgesic prescriptions.

Proportion of days covered

The proportion of individuals receiving an opioid analgesic was higher among PLWH compared to individuals without HIV. After weighting by IPTW and IPCW, the proportion of PLWH receiving at least one opioid prescription increased from 43.9% in 2001 to 49.6% in 2009. The corresponding proportion among patients without HIV was 29.0% in 2001 and 40.1% in 2009 (Table 2).

Not only were PLWH more likely to receive opioid prescriptions, but when examining only patients who received at least one opioid prescription, PLWH also had a higher proportion of total days covered (PDC) by an opioid. The PDC increased each year, from a mean of 0.24 among PLWH and 0.19 among people without HIV in 2001 to 0.34 and 0.28 in 2009 among patients with and without HIV, respectively (Figure 4). The PDC was slightly higher among the diabetic subset, as seen in the right panel of Figure 4.

Overall, more individuals received non-opioid analgesic prescriptions compared to opioid analgesics; however, like the opioid analgesic prescriptions, a higher proportion of PLWH received non-opioid analgesics compared to individuals without HIV. In the weighted study sample, 54.8% of PLWH and 39.4% of individuals without HIV received a non-opioid analgesic in 2001. By 2009, 59.4% and 51.6% of PLWH and individuals without HIV, respectively, received a non-opioid analgesic (Table 3).

Compared to the PDC of opioid analgesics, the difference in PDC for non-opioid analgesic prescriptions between PLWH and individuals without HIV was less pronounced. When looking at patients who received at least one non-opioid analgesic in the weighted study sample, the mean PDC for non-opioids among PLWH increased from 0.33 in 2001 to 0.43 in 2009. Among individuals without HIV, the mean PDC increased from 0.35 in 2001 to 0.41 in 2009. Mean and median PDC values both increased when we restricted the sample to diabetic patients only. Figure 5 provides more detail on the trends in PDC for non-opioid analgesic prescriptions.

Proportion of days covered: stratified

We stratified the PDC analysis for opioid prescriptions to determine whether the trends vary by age, sex, and/or state of residence. As above, we applied IPTW and IPCW to account for differences in comorbidities and Medicaid dropout by HIV status. Figure 6 displays the proportion of days covered by age category, with Table 4 describing the sample size depicted in the figure. Figure 7 (and Table 5) show trends by sex, and Figure 8 (and Table 6) shows the trends by state.

The highest proportion of PLWH receiving at least one opioid were aged 35-55 years (approximately 45% in 2001 and 51.5% in 2009), whereas the highest proportion of patients without HIV who received at least one opioid prescription were 45-64 years old (36.9% in 2001 and 45.2% in 2009) (Table 4). Among those receiving at least one opioid prescription, the distribution of the proportion of days covered was highest among patients aged 45-55 years, regardless of HIV status (mean among PLWH: 0.31 in 2001 to 0.41 in 2009; mean among people without HIV: 0.25 in 2001 to 0.34 in 2009). The lowest proportion of days covered occurred among patients between the ages of 18 and 35 years (mean among PLWH: 0.15 in 2001 to 0.25 in 2009; mean among people without HIV: 0.09 in 2001 to 0.19 in 2009). Figure 6 shows trends in the distribution of PDC by HIV status in the four age categories.

Females were more likely than males to receive an opioid analgesic, regardless of HIV status. In 2001, 47.1% of females with HIV and 30.6% of females without HIV received at least one opioid prescription, compared to 38.7% and 27.4% of males with and without HIV, respectively. In 2009, the proportion of females with and without HIV receiving at least one opioid prescription increased to 51.8% and 43.6%, respectively. Among males, the proportion increased to 46.5% and 36.6% among those with and without HIV, respectively (Table 5). Despite being more likely to receive an opioid prescription, women did not have a higher PDC compared to men. Among females receiving at least one opioid prescription, the mean PDC in 2001 was 0.22 among PLWH and 0.17 among women without HIV, and increased to 0.31 among PLWH and 0.26 among women without HIV in 2009 (Figure 7, left panel). Among males receiving at least one opioid prescription, the mean PDC among people with and without HIV was 0.26 and 0.22, respectively, in 2001 and increased to 0.38 and 0.30, respectively, in 2009 (Figure 7, right panel).

Among our sample of 12 states (Ohio was excluded due to missing data on opioid days supplied), there was considerable variation both in the proportion of individuals with at least one opioid prescription and in the PDC among those with at least one opioid prescription. Generally, the proportion of individuals receiving at least one opioid prescription increased over time, and the proportion PLWH receiving at least one opioid prescription was higher than the proportion among individuals without HIV. Table 6 shows the proportion of individuals in each state receiving at least one opioid prescription by year; it is important to note the small sample size (particularly among the PLWH group) in some states, including Alabama, Colorado, Pennsylvania, and Washington. As seen in Figure 8, the PDC among individuals with at least one opioid prescription was usually larger in among PLWH; however, the reverse was true in Alabama, Georgia, North Carolina, Maryland, and occasionally Pennsylvania and Texas.

Incident chronic opioid therapy

We selected a 10% random sample containing 456,199 individuals enrolled in 2001 as the analytic sample for the incidence of COT. Of these individuals, 110,565 (24.2%) were prevalent opioid users in 2001 and were excluded from the analysis. We excluded an additional 121,837 individuals with no follow-up after 2001. The final analytic sample for the incident COT analysis included 223,797 opioid-naïve individuals who contributed 940,329 person-years of follow-up. The diabetic subset contained 13,383 patients who contributed 78,376 person-years of follow-up.

Overall, 9,049 individuals (4.0%) progressed to COT during the 8-year follow-up period for an incidence rate of 9.6 per 1,000 person-years. Among PLWH, 448 individuals (incidence rate: 29.1 per 1,000 person-years) developed COT compared to 8,601 individuals without HIV (incidence rate: 9.3 per 1,000 person-years). Among patients with diabetes, 2,246 individuals (16.8%) progressed to COT for an incidence rate of 28.7 per 1,000 person-years; 69 of whom were living with HIV (incidence rate: 43.7 per 1,000 person-years) compared to 2,177 without HIV (incidence rate: 28.3 per 1,000 person-years). Figure 9 and Figure 10 show the Kaplan-Meier estimated cumulative incidence of COT by HIV status, weighted by IPCW, for the full and diabetic subsamples, respectively.

In an IPCW-weighted unadjusted Cox proportional hazards model, people with HIV had 3.06 times the hazard for COT compared to patients without HIV (95% CI 2.76-3.39). After adjusting for age, sex, and state of residence, the increased hazard among people living with HIV decreased to 2.37 (95% CI 2.13-2.63). Further adjusting for major ADG count, bipolar disorder, depression, and schizophrenia, the hazard ratio comparing PLWH to patients without HIV was 1.46 (95% CI 1.31-1.63). The results of the Cox proportional hazards models are shown in Table 7.

Among the weighted subset of individuals with diabetes, PLWH had 1.61 (95% CI 1.25-2.09) times the hazard of COT compared to diabetics without HIV in an unadjusted Cox proportional hazards model. The hazard was slightly higher after adjusting for age, sex, and state of residence (aHR=1.72, 95% CI 1.32-2.23), but became smaller and statistically non-significant after further adjusting for major ADG count, bipolar disorder, depression, and schizophrenia (aHR=1.26, 95% CI 0.97-1.63). Table 8 shows the results of the Cox proportional hazards models among the subset of patients with diabetes.

Discussion

In our sample of approximately 4.5 million Medicaid enrolled individuals, we found an increasing rate of all prescription oral analgesics, both opioid and non-opioid, from 2001 and 2009 regardless of HIV status. The annual number of opioid prescriptions dispensed at the start of our study averaged to slightly more than one per person among the HIV uninfected population and approximately 2.5 per person among PLWH in 2001, and increased to approximately 2 per person among HIV uninfected individuals and nearly 4 per person among PLWH in 2009. The dramatic increase in opioid dispensing is concerning, as an increase in the availability of opioids may lead to an increased rate of opioid abuse and overdose.

Not only did we find an increase in opioid prescriptions, but we also found a similar increase in non-opioid analgesic prescriptions over the same time period. This may be a reflection of providers first prescribing non-opioid analgesics to patients requesting opioid treatment for pain. The similar increase in all analgesic prescriptions may also reflect a secular trend in the United States towards pharmaceuticals. As interventions are being implemented across the United States to reduce inappropriate opioid prescribing and reduce the consequences of opioid misuse, we would hope to observe an increase in non-opioid analgesics with a simultaneous decrease in opioid prescriptions as providers tend towards non-opioid treatments.

In all years, PLWH received a higher number of analgesic prescriptions compared to individuals without HIV. However, the characteristics of PLWH and individuals without HIV varied considerably. Weighting the study population and restricting the sample to patients with diabetes helped to reduce heterogeneity in the sample, and also diminished the differences in number of analgesic prescriptions, suggesting that the differential prescription rates may be due largely to differences in age, sex, and co-morbidities between the populations. Our weighted diabetic subsample was designed to further remove heterogeneity by HIV status, allowing us to assume approximately equal rates of chronic pain in the two comparison groups. Because we found similar, and even slightly higher, rates of analgesic prescriptions among PLWH after accounting for demographic and clinical characteristics, we do not have evidence to support a systematic under-treatment of pain among PLWH.

The distribution of opioids dispensed is highly skewed, with a large proportion of individuals receiving no prescriptions, and small proportion (top 25th percentile of those receiving at least one prescription) receiving very high numbers of opioids. Even when excluding individuals who received no opioid prescriptions (all boxplots were restricted to patients with at least one opioid prescription), the median PDC was notably smaller than the mean across all years and all strata. The skewed distribution is important to note when interpreting the number of analgesics dispensed per 100 individuals, as the high number of prescriptions dispensed to the few individuals who receive the most prescriptions affects the standardized rate of opioid prescriptions.

Compared to a recently published study examining trends in opioid prescribing between 2006-2016[19], we observed a higher number of opioids prescribed per capita. This is likely due in part to the characteristics of our study population: specifically, that our study population was drawn from a population of Medicaid-enrolled individuals who have higher rates of co-morbidities compared to the general population. Despite finding higher absolute numbers of prescriptions per capita than the 2017 publication, the trends we observed regarding the dramatic increase in prescribing rates through 2009 were consistent. Because of the similar trajectory we observed in our population compared to recently measured trends, we would expect to see a similar stabilization in opioid prescriptions among Medicaid enrolled PLWH beyond 2009, if we were to extrapolate the trends beyond the timeframe of this analysis.

Trends by age and sex were consistent throughout our study, with females being more likely to receive an opioid prescription and having a statistically significant higher incidence of COT compared to males. We observed a higher prevalence of opioid use and a higher incidence of COT among individuals who were older at study baseline. These trends by age and sex, are consistent with prior literature on opioid dispensing patterns across the United States[24,25], although they differ from trends examining opioid misuse and overdose, supporting studies that report additional characteristics on the causal pathway between receiving an opioid prescription and developing opioid misuse[26]. In other words, receiving a larger quantity of opioids is not, in itself, sufficient to predict an increased likelihood for misuse.

We observed significant variability in opioid prescribing trends by state, which follows logically due to the varying Medicaid eligibility requirements by state (resulting in demographic, socioeconomic, and clinical differences in the analytic sample by state) and also to differences in state policies regarding opioid prescribing, namely prescription drug monitoring programs. In a 2006 study of geographic variability in opioid prescribing, Curtis et al. also found significant variation in rates of opioid prescriptions across the United States[11], though the population analyzed in this study comprised commercially insured individuals, resulting in slightly different trends than we observed in our Medicaid-enrolled sample. McDonald et al. also found higher than expected variation in opioid prescribing between states, with more opioids being prescribed in Appalachian, southern, and western states[27]. Zerzan et al., who also studied opiate use among a Medicaid population, report large increases in opioid prescriptions between 1996-2002 and found unexplained geographic variation[28].

Developing chronic opioid use was fairly uncommon among all opioid-naïve individuals, which is consistent with prior literature[24], but it was significantly more likely among PLWH compared to individuals without HIV. The increased hazard for COT among PLWH persisted, though the magnitude decreased, after adjusting for demographic and clinical characteristics and diminished even further when we restricted the sample to patients with diabetes. These findings suggest that the increased hazard of COT among PLWH is due primarily to differences in co-morbidities among PLWH and disparities in people who acquired HIV during the timeframe of our study. In other words, we did not find evidence to suggest differential treatment among patients by HIV status alone; however, we did find that PLWH are more likely than the general population to have chronic conditions requiring COT. Awareness about the proper treatment of pain among PLWH and recommendations for appropriate opioid prescribing are important in the treatment of PLWH.

The sample of PLWH included in our analysis differs from the general population of PLWH across the United States. Most notably, our sample of PLWH was nearly 50% female, whereas the US population of PLWH is approximately 25% female[29]. The overrepresentation of women in our study sample is likely due to Medicaid's more lenient eligibility requirements during pregnancy and the increased likelihood for single mothers with dependents to meet the income threshold for Medicaid enrollment. Because our study population includes only Medicaid-enrolled individuals, our results are most applicable to populations of lower socioeconomic status rather than all PLWH. Further, our study sample was unique in that we analyzed a closed cohort of individuals who were continuously enrolled in Medicaid during our follow-up period. It is possible that the characteristics of individuals who remained in our study differ from those of a dynamic Medicaid population.

There were some limitations to this study. First, we were limited in our ability to examine absolute trends in opioid prescriptions over time, as our sample was drawn from a closed cohort of Medicaid-enrollees. However, the primary focus of this analysis was to compare trends by HIV status, so the absence of data on the absolute number of prescriptions is did not preclude the analysis. Next, we were unable to measure the prevalence of a large portion of non-opioid analgesics, as a majority of non-opioid analgesics are purchased over-the-counter and do no appear in Medicaid prescription claims files. Similarly, we did not know the indication for the non-opioid analgesics prescribed; many of the non-opioid analgesics included in the analysis have non-pain related indications and are only occasionally used off-label to treat pain. We report the proportion of the non-opioid analgesics included in the analysis that is primarily used for pain (i.e. NSAIDs) versus anticonvulsants, anti-depressants, and muscle relaxants in Supplementary Table 4.

Despite the limitations, our study also incorporated several strengths. First, we analyzed a large sample of patients and were able to examine a comprehensive list of all prescriptions dispensed to our study sample. The closed cohort allowed us to follow the same individuals over time, enabling the examination of progression to COT among opioid-naïve individuals. Also, despite being unable to measure over-the-counter medications, we did attempt to account for alternative analgesic treatments by examining prescription non-opioid analgesic medications. Finally, by using only Medicaid-eligible participants (Medicaid eligibility criteria varies by state, but in all cases requires individuals to earn below a threshold income, often below 138% of the federal poverty level[30]), we restricted our population to a particular socioeconomic subset of the US population that was of interest for this study. This helps mitigate residual confounding that was likely present due to our inability to adjust for unmeasured socio-demographic and behavioral characteristics.

Overall, the trends we observed in analgesic prescription rates do not support an under-treatment of pain among PLWH. In fact, we found that PLWH were more likely to receive opioid analgesics and, when they did receive opioids, they received greater numbers than individuals without HIV. The increased proportion of days covered by an opioid among PLWH may be due to a higher prevalence of pain in these individuals; however, the similarity by HIV status in the standardized number of opioid prescriptions after accounting for demographic and clinical differences, and the higher incidence of COT among PLWH after adjustment for confounders suggest that PLWH receive at least equal, if not greater, opioid therapy compared to their HIV-uninfected counterparts. Pain is highly prevalent among PLWH; focusing on the appropriate treatment of chronic pain, especially among PLWH with a history of substance abuse, is an important component to managing HIV.

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Table 1: Baseline demographic characteristics

Characteristics of the analytic study sample in 2001 by HIV status; N=4,561,139

	N (%)	
	HIV N=54,120	**Non-HIV N=4,507,019**
Age, median (IQR)	42 (37, 48)	34 (25, 45)
Sex		
Female	25,414 (46.96)	3,291,573 (73.03)
Male	28,705 (53.04)	1,215,429 (26.97)
State		
Alabama	427 (0.79)	114,118 (2.53)
California	6,674 (12.33)	1,673,938 (37.14)
Colorado	106 (0.20)	38,021 (0.84)
Florida	6,379 (11.79)	326,491 (7.24)
Georgia	1,780 (3.29)	121,603 (2.70)
Illinois	2,606 (4.82)	252,942 (5.61)
Massachusetts	2,480 (4.58)	263,398 (5.84)
Maryland	2,588 (4.78)	131,057 (2.91)
North Carolina	1,619 (2.99)	142,488 (3.16)
New York	23,949 (44.25)	609,068 (13.51)
Ohio	907 (1.68)	241,346 (5.35)
Pennsylvania	1,931 (3.57)	282,882 (6.28)
Texas	2,353 (4.35)	201,426 (4.47)
Washington	321 (0.59)	108,241 (2.40)
Opioid prevalent		
No	31,628 (58.44)	3,421,929 (75.92)
Yes	22,492 (41.56)	1,085,090 (24.08)
Major ADG count		
0	36,280 (67.04)	4,1911,135 (93.0)
1	5,907 (10.91)	193,922 (4.30)
2	6,521 (12.05)	78,267 (1.74)
3+	5,412 (10.00)	43,695 (0.97)
Diabetes	4,540 (8.39)	283,487 (6.29)
Depression	21,022 (38.84)	767,935 (17.04)
Bipolar	625 (1.15)	18,242 (0.40)
Schizophrenia	1,568 (2.90)	41,478 (0.92)

Table 2: Number and proportion of individuals with at least one prescription opioid analgesic in each year, among full sample and diabetic subset, weighted

		2001	2002	2003	2004	2005	2006	2007	2008	2009
Full Sample										
HIV	N	15,924.6	12,270.5	13,986.4	15,540.5	16,862.9	18,339.1	19,773.2	20,636.3	21,393.8
	%	43.90	40.92	42.24	43.65	44.87	45.63	47.17	48.92	49.55
No HIV	N	12,317.1	9,820.8	12,047.4	14,081.7	16,123.5	18,278.9	19,869.0	20,892.8	22,220.7
	%	28.99	29.39	31.32	33.07	35.19	36.51	37.36	38.79	40.09
Diabetic subset										
HIV	N	1,563.2	1,363.8	1,744.8	2,163.2	2,538.6	2,987.8	3,504.9	3,837.2	4,154.3
	%	51.69	48.42	48.35	49.70	50.80	51.51	53.89	55.81	57.14
No HIV	N	2,428.5	2,079.5	2,824.1	3,528.9	4,241.1	5,092.0	5,815.3	6,198.9	6,579.5
	%	47.62	45.26	46.68	47.97	49.59	50.63	51.30	52.38	53.46

Table 3: Number and proportion of individuals with at least one prescription non-opioid analgesic in each year, among full sample and diabetic subset, weighted

		2001	2002	2003	2004	2005	2006	2007	2008	2009
Full Sample										
HIV	N	19,874.1	16,483.9	18,555.1	20,423.7	21,627.8	22,934.1	24,320.7	24,878.1	25,645.9
	%	54.79	54.97	56.03	57.37	57.55	57.07	58.02	58.97	59.40
No HIV	N	16,735.4	14,314.1	17,469.1	20,240.6	22,419.3	24,682.1	26,536.8	27,330.2	28,553.9
	%	39.38	42.84	45.41	47.53	48.93	49.30	49.90	50.74	51.56
Diabetic subset										
HIV	N	2,042.3	1,893.7	2,444.8	3,010.7	3,436.8	3,980.4	4,543.1	4,854.5	5,147.7
	%	67.53	67.23	67.64	69.17	68.78	68.63	69.85	70.61	70.80
No HIV	N	3,379.8	3,070.2	4,119.0	5,132.6	5,902.6	6,782.6	7,681.8	8,052.8	8,392.2
	%	66.28	66.82	68.09	69.77	69.02	67.44	67.77	68.04	68.19

Table 4: Number and proportion of individuals with at least one prescription opioid analgesic in each year, by age at baseline, weighted

		2001	2002	2003	2004	2005	2006	2007	2008	2009
Age 18-34 at baseline										
HIV	N	3,910.0	2,876.4	3,434.2	4,002.9	4,535.6	5,145.5	5,616.6	6,187.4	6,727.7
	%	43.29	39.28	40.22	41.49	42.56	43.16	44.23	46.06	46.57
No HIV	N	3,434.9	2,645.5	3,257.1	3,868.2	4,610.4	5,426.5	5,880.8	6,636.5	7,614.0
	%	20.37	21.78	23.61	25.39	27.81	29.23	30.00	32.13	34.20
Age 35-44 at baseline										
HIV	N	7,026.0	5,450.0	6,302.6	6.953.2	7,548.7	8,211.4	8,960.5	9,332.9	9,733.1
	%	45.01	41.64	43.72	44.85	46.13	46.99	48.92	50.58	51.54
No HIV	N	2,719.3	2,390.3	3,021.9	3,652.0	4,346.8	5,091.7	5,752.1	6,278.0	6,911.0
	%	30.53	30.20	32.35	34.10	36.57	38.05	39.26	41.23	42.77
Age 45-54 at baseline										
HIV	N	4,129.0	3,318.8	3,599.6	3,932.0	4,170.4	4,442.9	4,759.1	4,864.0	4,849.3
	%	44.04	41.85	42.33	44.29	45.59	46.40	47.83	49.81	50.25
No HIV	N	3,206.2	2,752.9	3,526.0	4,272.1	5,004.1	5,909.1	6,686.1	7,027.6	7,346.5
	%	36.88	35.95	37.82	39.51	41.36	42.61	43.50	44.39	45.24
Age 55-64 at baseline										
HIV	N	859.5	625.4	650.0	652.4	608.1	539.3	436.0	252.0	82.6
	%	38.10	37.99	39.24	41.50	43.08	44.40	46.10	47.36	43.83
No HIV	N	2,956.7	2,032.0	2,242.2	2,289.2	2,161.8	1,950.9	1,548.9	949.4	327.9
	%	36.82	35.69	37.33	39.34	41.12	42.51	43.61	44.29	46.00

Table 5: Number and proportion of individuals with at least one prescription opioid analgesic in each year, by sex, weighted

		2001	2002	2003	2004	2005	2006	2007	2008	2009
Female										
HIV	N	8,231.3	5,975.3	7,034.5	7,898.6	8,830.1	9,566.4	10,471.3	11,155.6	11,742.0
	%	47.06	43.47	44.70	45.45	47.14	47.06	48.92	50.78	51.78
No HIV	N	6,509.0	5,081.9	6,367.4	7,519.7	8,645.6	9,814.6	10,600.3	11,274.9	12,104.2
	%	30.61	32.13	33.99	35.61	38.03	39.71	40.58	42.15	43.59
Male										
HIV	N	7,693.3	6,295.3	6,952.0	7,642.0	8,032.8	8,772.7	9,301.9	9,480.6	9,651.9
	%	38.70	38.27	39.30	41.13	41.86	43.32	44.40	46.07	46.45
No HIV	N	5,808.1	4,738.9	5,680.0	6,562.1	7,478.0	8,464.3	9,268.6	9,618.0	10,096.6
	%	27.36	26.93	28.78	30.57	32.39	33.39	34.26	35.47	36.57

Table 6: Number and proportion of individuals with at least one prescription opioid analgesic in each year, by state, weighted

		2001	2002	2003	2004	2005	2006	2007	2008	2009
Alabama										
HIV	N	124.8	142.8	167.6	199.2	213.1	238.6	258.6	262.4	293.5
	%	54.01	50.22	52.73	55.24	55.72	58.45	61.37	61.70	64.22
No HIV	N	112.0	130.5	166.2	199.1	214.6	244.6	264.8	261.2	260.5
	%	41.04	40.38	40.74	41.26	42.83	53.30	56.09	55.43	56.01
California										
		2001	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**
HIV	N	1,984.3	2,497.7	2,883.3	3,086.2	3,213.4	3,533.6	3,892.4	3,947.0	3,862.4
	%	50.58	53.06	54.06	53.74	52.70	54.07	55.20	55.69	53.39
No HIV	N	1,228.1	1,484.7	1,946.5	2,189.4	2,249.2	2,559.3	2,857.6	2,962.6	2,919.5
	%	24.35	24.85	28.06	30.14	30.36	32.04	33.66	35.45	35.64
Colorado										
		2001	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**
HIV	N	32.0	25.3	30.7	42.9	54.3	59.5	73.9	66.2	65.2
	%	52.83	37.44	38.96	50.61	54.29	48.09	56.71	51.48	47.91
No HIV	N	19.0	21.7	36.6	40.5	45.4	58.2	71.1	76.7	77.8
	%	25.11	25.75	34.69	37.10	37.00	43.78	47.19	50.13	49.62
Georgia										
		2001	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**
HIV	N	543.6	578.5	694.6	779.9	802.8	843.6	812.0	942.5	1,011.9
	%	53.81	51.68	56.34	57.87	57.00	57.26	53.87	59.54	60.64
No HIV	N	542.6	618.4	816.7	965.9	1,035.2	1,095.8	1,054.9	1,194.1	1,258.0
	%	50.92	52.39	56.04	56.65	57.63	57.18	52.02	58.36	60.46
Illinois										
		2001	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**
HIV	N	613.5	681.5	768.7	842.5	909.8	976.4	1,024.3	1,089.0	1,153.8
	%	43.52	43.18	45.00	45.64	46.73	47.95	47.81	47.86	50.13
No HIV	N	459.6	576.4	729.0	872.5	954.6	1,083.9	1,194.7	1,390.9	1,519.4
	%	30.88	36.72	39.08	40.86	41.84	43.31	44.71	42.57	46.07
Massachusetts										
		2001	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**
HIV	N	652.9	762.9	817.1	938.3	1,047.6	1,186.4	1,303.8	1,297.5	1,374.5
	%	47.00	46.74	45.21	46.49	47.53	48.66	50.50	49.80	49.71
No HIV	N	580.5	602.9	641.7	766.6	878.4	992.7	1,147.1	1,142.6	1,227.3
	%	30.74	31.13	32.19	32.66	33.75	33.77	35.71	35.68	36.62
Maryland										
		2001	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**
HIV	N	646.6	698.1	655.8	801.1	986.7	1,138.6	1,353.3	1,428.1	1,566.0
	%	43.87	42.28	37.18	42.66	47.94	50.48	56.58	58.84	61.17
No HIV	N	496.9	570.9	585.2	748.0	1,014.9	1,199.1	1,357.5	1,475.2	1,743.9
	%	27.89	29.75	27.41	32.04	38.72	43.09	47.38	51.14	54.17
North Carolina										
		2001	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**
HIV	N	488.6	546.2	602.7	648.2	676.2	695.9	798.9	841.7	891.8
	%	53.02	54.22	56.50	57.10	57.96	56.15	61.09	62.07	65.12
No HIV	N	480.7	567.4	697.5	802.1	872.0	1,007.4	1,080.1	1,107.3	1,143.2
	%	51.29	53.85	55.52	57.70	59.49	60.24	60.69	62.14	62.37

New York										
		2001	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**
HIV	N	4,253.4	4,967.1	5,878.2	6,560.5	7,288.0	7,867.4	8,403.4	8,980.6	9,392.3
	%	33.40	33.83	35.93	37.33	39.39	39.83	41.43	44.46	45.82
No HIV	N	3,293.3	4,042.4	4,940.7	5,794.3	7,002.7	7,890.1	8,638.3	9,207.9	9,971.3
	%	24.78	25.15	26.89	28.46	31.42	32.27	33.32	35.18	36.69
Pennsylvania										
		2001	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**
HIV	N	180.5	114.2	89.2	97.8	111.2	103.3	115.3	117.6	123.6
	%	17.61	12.23	9.66	10.27	11.35	10.42	11.63	12.31	12.97
No HIV	N	122.1	116.9	126.2	148.4	161.0	186.9	211.4	212.4	217.6
	%	14.75	13.47	12.47	12.95	13.08	13.86	14.55	14.88	15.17
Texas										
		2001	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**
HIV	N	673.3	817.6	917.4	1,014.0	994.8	1,080.0	1,223.0	1,244.6	1,256.5
	%	49.27	52.50	54.16	57.27	55.23	56.19	58.99	59.40	59.62
No HIV	N	632.4	749.1	920.9	1,036.5	1,104.2	1,259.6	1,470.4	1,449.8	1,495.6
	%	42.97	46.06	47.63	48.10	49.02	50.39	51.84	51.38	53.26
Washington										
		2001	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**
HIV	N	114.8	108.9	134.6	152.2	158.1	188.9	213.3	193.1	183.3
	%	56.68	51.74	54.55	56.11	56.06	58.62	59.24	52.81	43.56
No HIV	N	70.7	75.1	107.0	127.1	144.0	221.7	233.9	222.9	176.9
	%	29.00	29.80	33.75	34.35	36.38	51.05	52.42	51.99	36.36

Table 7: Development of chronic opioid therapy among opioid-naïve individuals

Cox proportion hazards model for the development of chronic opioid therapy among opioid-naïve individuals between January 1, 2002 and December 31, 2009; sample selected from a 10% random sample of eligible study population; N=223,797 individuals contributing 940,329 person-years of follow-up. Adjusted Model 1: adjusted for categorical age, sex, and state of residence (Ohio excluded due to missing data on opioid days supplied). Adjusted Model 2: adjusted for categorical age, sex, state of residence, major ADG count, bipolar disorder, schizophrenia, and depression. All models weighted by the inverse probability of censoring.

	Hazard Ratio (95% CI)		
	Unadjusted Model	**Adjusted Model 1**	**Adjusted Model 2**
HIV	3.06 (2.76-3.39)	2.37 (2.13-2.63)	1.46 (1.31-1.63)
Age			
18 to <35		Ref	Ref
35 to <45	--	2.65 (2.50-2.80)	2.05 (1.94-2.17)
45 to <55		4.09 (3.87-4.32)	2.67 (2.52-2.83)
55 to <65		4.85 (4.49-5.23)	2.98 (2.76-3.22)
Sex			
Male	--	Ref	Ref
Female		1.28 (1.22-1.34)	1.15 (1.09-1.20)
State of residence			
Alabama		Ref	Ref
California		0.58 (0.52-0.65)	0.66 (0.58-0.74)
Colorado		1.52 (1.29-1.81)	1.74 (1.47-2.06)
Georgia		0.94 (0.81-1.10)	0.86 (0.73-1.00)
Illinois		0.76 (0.66-0.87)	0.67 (0.59-0.77)
Massachusetts	--	0.65 (0.57-0.75)	0.59 (0.52-0.68)
Maryland		0.78 (0.66-0.92)	0.69 (0.59-0.81)
North Carolina		1.17 (1.01-1.35)	1.05 (0.91-1.22)
New York		0.69 (0.61-0.78)	0.62 (0.55-0.70)
Pennsylvania		0.22 (0.19-0.26)	0.41 (0.35-0.48)
Texas		1.06 (0.92-1.21)	0.93 (0.81-1.06)
Washington		0.71 (0.59-0.86)	0.68 (0.56-0.82)
Major ADG count			
0			Ref
1	--	--	2.53 (2.35-2.73)
2			3.32 (3.06-3.60)
3+			5.15 (4.76-5.58)
Bipolar disorder	--	--	0.83 (0.73-0.94)
Schizophrenia	--	--	0.41 (0.38-0.46)
Depression	--	--	4.28 (4.08-4.49)

Table 8: Development of chronic opioid therapy among opioid-naïve diabetics

Cox proportion hazards model for the development of chronic opioid therapy among opioid-naïve diabetics between January 1, 2002 and December 31, 2009; sample selected from a 10% random sample of eligible study population; weighted by inverse probability of censoring weights; N=13,383 individuals contributing 78,376 person-years of follow-up. Adjusted Model 1: adjusted for categorical age, sex, and state of residence (Ohio excluded due to missing data on opioid days supplied). Adjusted Model 2: adjusted for categorical age, sex, state of residence, major ADG count, bipolar disorder, schizophrenia, and depression. All models weighted by the inverse probability of censoring.

	Hazard Ratio (95% CI)		
	Unadjusted Model	**Adjusted Model 1**	**Adjusted Model 2**
HIV	1.61 (1.25-2.09)	1.72 (1.32-2.23)	1.26 (0.97-1.63)
Age			
18 to <35		Ref	Ref
35 to <45	--	1.72 (1.48-1.99)	1.60 (1.38-1.85)
45 to <55		1.98 (1.72-2.28)	1.74 (1.51-2.00)
55 to <65		1.96 (1.66-2.31)	1.72 (1.46-2.03)
Sex			
Male	--	Ref	Ref
Female		1.22 (1.11-1.33)	1.14 (1.04-1.25)
State of residence			
Alabama		Ref	Ref
California		0.58 (0.47-0.73)	0.65 (0.52-0.82)
Colorado		1.78 (1.26-2.51)	1.72 (1.22-2.43)
Georgia		0.75 (0.55-1.01)	0.73 (0.54-0.99)
Illinois		0.74 (0.57-0.96)	0.72 (0.56-0.94)
Massachusetts	--	0.75 (0.57-0.99)	0.69 (0.52-0.92)
Maryland		0.70 (0.51-0.96)	0.67 (0.49-0.92)
North Carolina		0.85 (0.64-1.11)	0.88 (0.67-1.16)
New York		0.55 (0.44-0.70)	0.55 (0.44-0.70)
Pennsylvania		1.21 (0.89-1.64)	1.08 (0.79-1.46)
Texas		0.79 (0.62-1.02)	0.79 (0.62-1.02)
Washington		0.95 (0.65-1.37)	0.90 (0.62-1.30)
Major ADG count			
0			Ref
1	--	--	1.83 (1.59-2.10)
2			2.63 (2.30-3.00)
3+			3.55 (3.12-4.04)
Bipolar disorder	--	--	0.72 (0.57-0.92)
Schizophrenia	--	--	0.46 (0.38-0.54)
Depression	--	--	2.26 (2.06-2.49)

Figure 2: Opioid Analgesic Prescriptions per 100 People

Total number of opioid analgesic prescriptions dispensed between 2001-2009 per 100 people, by HIV status; left panel: full analytic sample; right panel: restricted to patients with diabetes only; dashed lines depict unadjusted trends; solid lines depict trends weighted by inverse probability of HIV weights and by the inverse probability of censoring

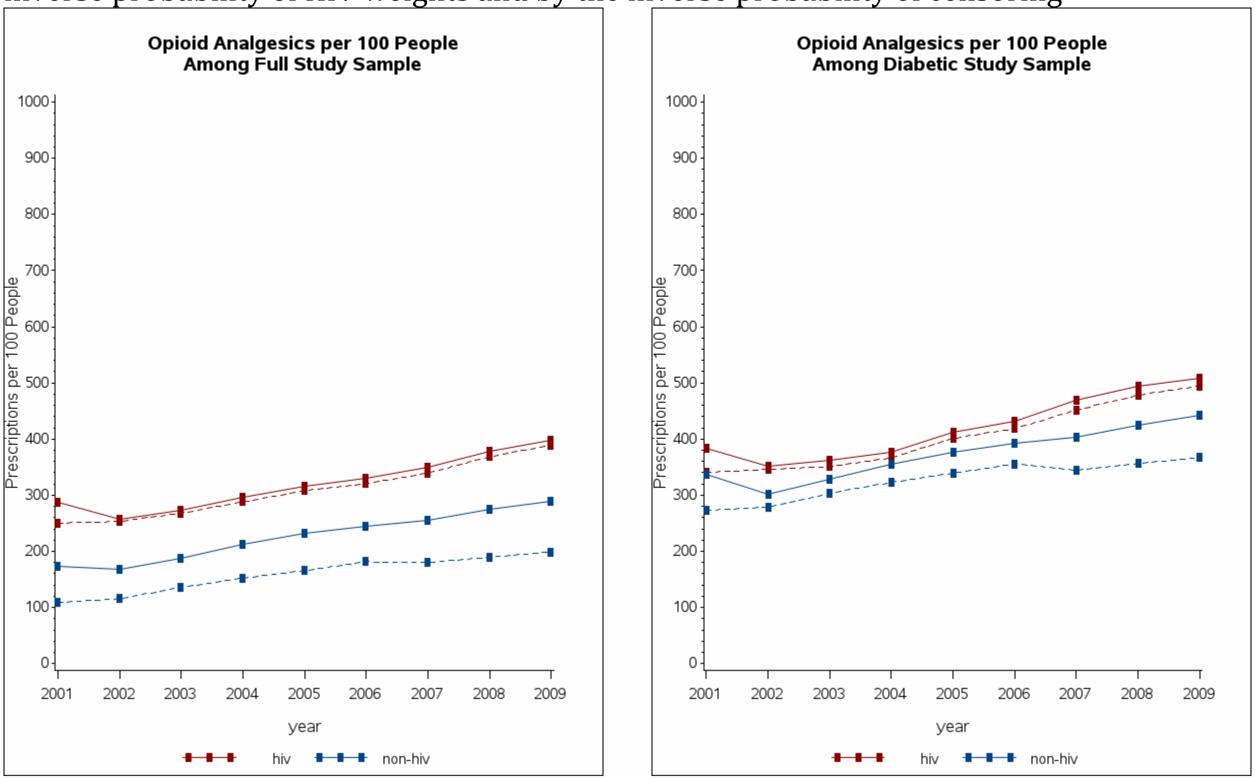


Figure 3: Non-Opioid Analgesic Prescriptions per 100 People

Total number of non-opioid analgesic prescriptions dispensed between 2001-2009 per 100 people, by HIV status; left panel: full analytic sample; right panel: restricted to patients with diabetes only; dashed lines depict unadjusted trends; solid lines depict trends weighted by inverse probability of HIV weights and by the inverse probability of censoring

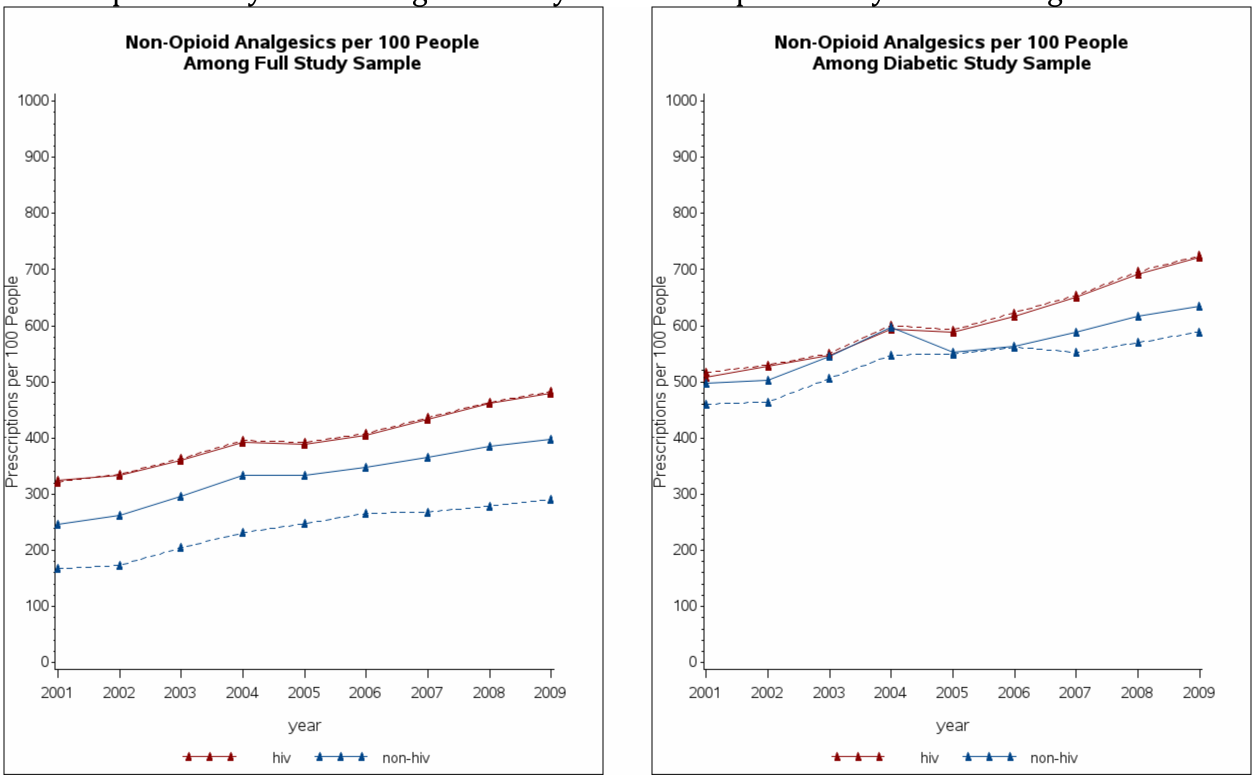


Figure 4: Proportion of Days Covered by an Opioid Analgesic, weighted

Proportion of days covered by an opioid analgesic prescription among individuals with at least one opioid analgesic prescription in the given year, weighted by inverse probability of HIV and by the inverse probability of censoring (left panel: all individuals; right panel: diabetic subset). The shaded box depicts the interquartile range, the whiskers indicate the minimum and maximum values, the horizontal line shows the median, and the open circle (HIV group) or cross (non-HIV group) shows the mean. The table below the x-axis displays the proportion of individuals in each year with at least one opioid prescription. Table 2 describes the sample size and overall proportion of individuals with an opioid in each year.

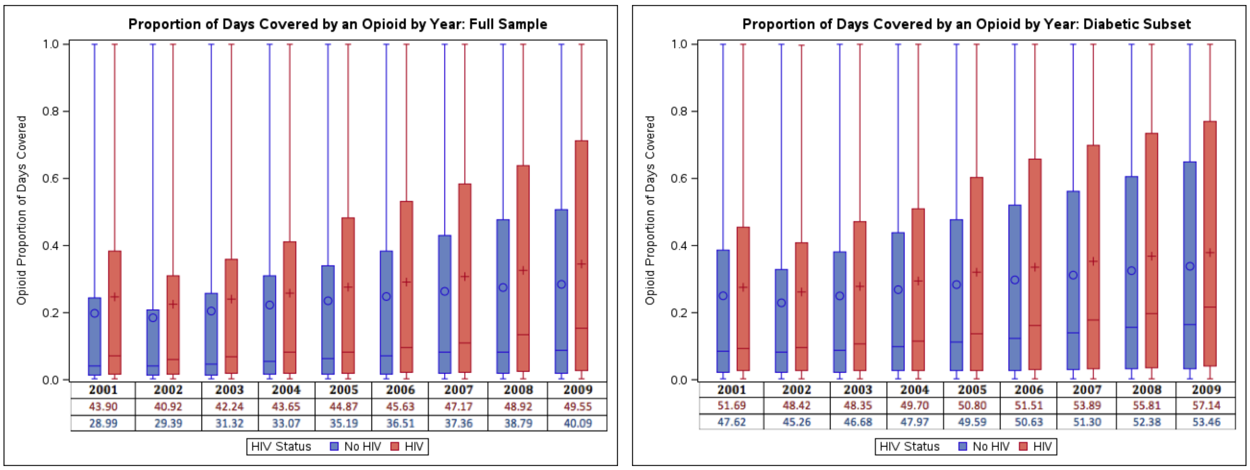


Figure 5: Proportion of Days Covered by a Non-Opioid Analgesic, weighted

Proportion of days covered by a non-opioid analgesic prescription among individuals with at least one non-opioid analgesic prescription in the given year, weighted by inverse probability of HIV and by the inverse probability of censoring (left panel: all individuals; right panel: diabetic subset). The shaded box depicts the interquartile range, the whiskers indicate the minimum and maximum values, the horizontal line shows the median, and the open circle (HIV group) or cross (non-HIV group) shows the mean. The table below the x-axis displays the proportion of individuals in each year with at least one non-opioid prescription. Table 3 describes the sample size and overall proportion of individuals with a non-opioid in each year.

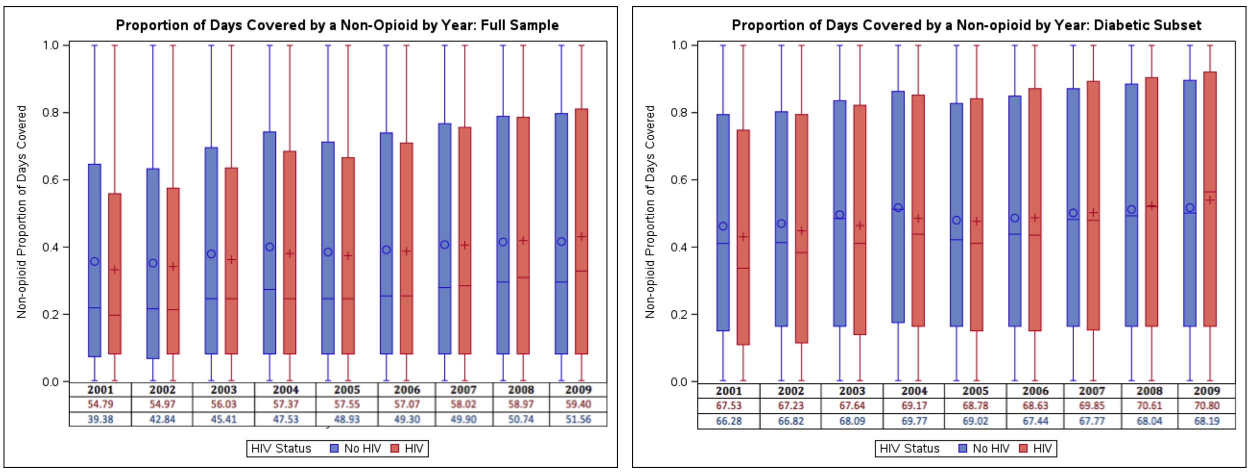


Figure 6: Proportion of Days Covered by an Opioid Analgesic, by age at baseline, weighted

Proportion of days covered by an opioid analgesic prescription among individuals with at least one opioid analgesic prescription in the given year, stratified by age at baseline, weighted by inverse probability of HIV and by the inverse probability of censoring. The shaded box depicts the interquartile range, the whiskers indicate the minimum and maximum values, the horizontal line shows the median, and the open circle (HIV group) or cross (non-HIV group) shows the mean. The table below the x-axis displays the proportion of individuals in each year with at least one opioid prescription. Table 4 describes the sample size and overall proportion of individuals with an opioid in each year.

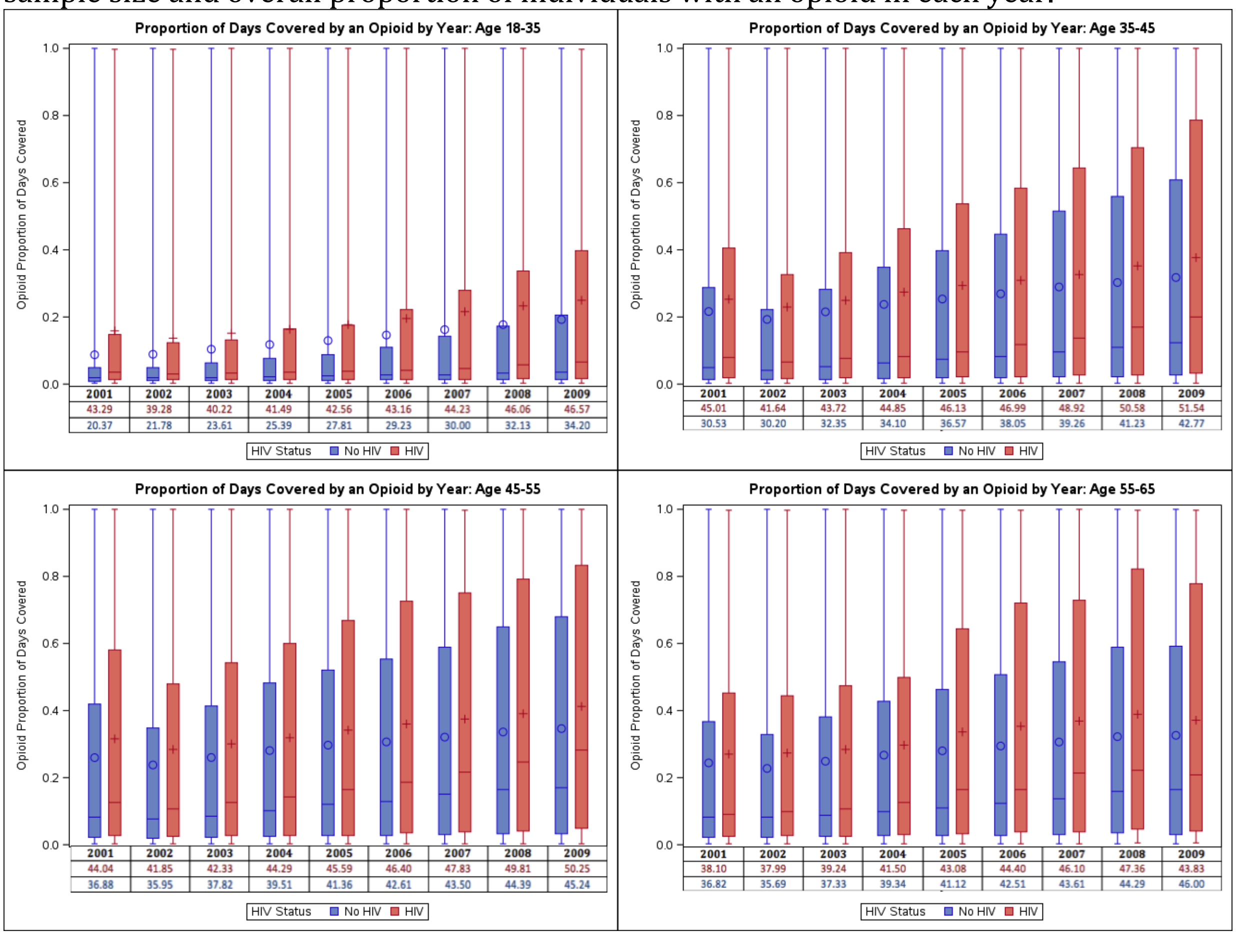


Figure 7: Proportion of Days Covered by an Opioid Analgesic, by sex, weighted

Proportion of days covered by an opioid analgesic prescription among individuals with at least one opioid analgesic prescription in the given year, stratified by sex, weighted by inverse probability of HIV and by the inverse probability of censoring. The shaded box depicts the interquartile range, the whiskers indicate the minimum and maximum values, the horizontal line shows the median, and the open circle (HIV group) or cross (non-HIV group) shows the mean. The table below the x-axis displays the proportion of individuals in each year with at least one opioid prescription. Table 5 describes the sample size and overall proportion of individuals with an opioid in each year.

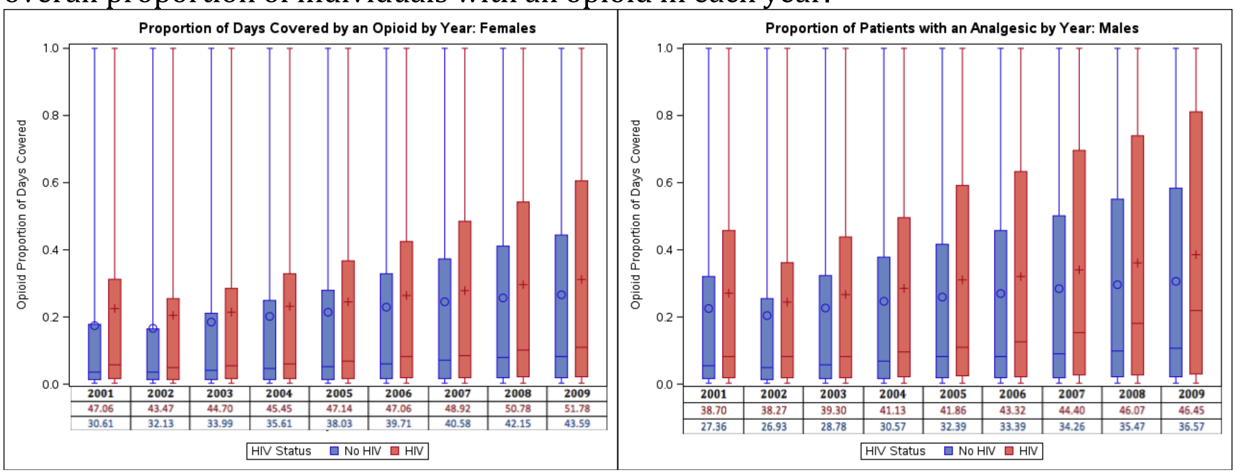


Figure 8: Proportion of Days Covered by an Opioid Analgesic, by state, weighted

Proportion of days covered by an opioid analgesic prescription among individuals with at least one opioid analgesic prescription in the given year, stratified by state of residence, weighted by inverse probability of HIV and by the inverse probability of censoring. The shaded box depicts the interquartile range, the whiskers indicate the minimum and maximum values, the horizontal line shows the median, and the open circle (HIV group) or cross (non-HIV group) shows the mean. The table below the x-axis displays the proportion of individuals in each year with at least one opioid prescription. Table 6 describes the sample size and overall proportion of individuals with an opioid in each year.

Figure 9: Kaplan-Meier estimate for the incidence of chronic opioid therapy, weighted

Cumulative incidence of the development of chronic opioid therapy (COT) among a sample of opioid-naïve individuals followed from January 1, 2002 until the first day of COT (defined as the 90th day of consecutive opioid use), Medicaid dis-enrollment, or December 31, 2009, weighted by inverse probability of censoring.

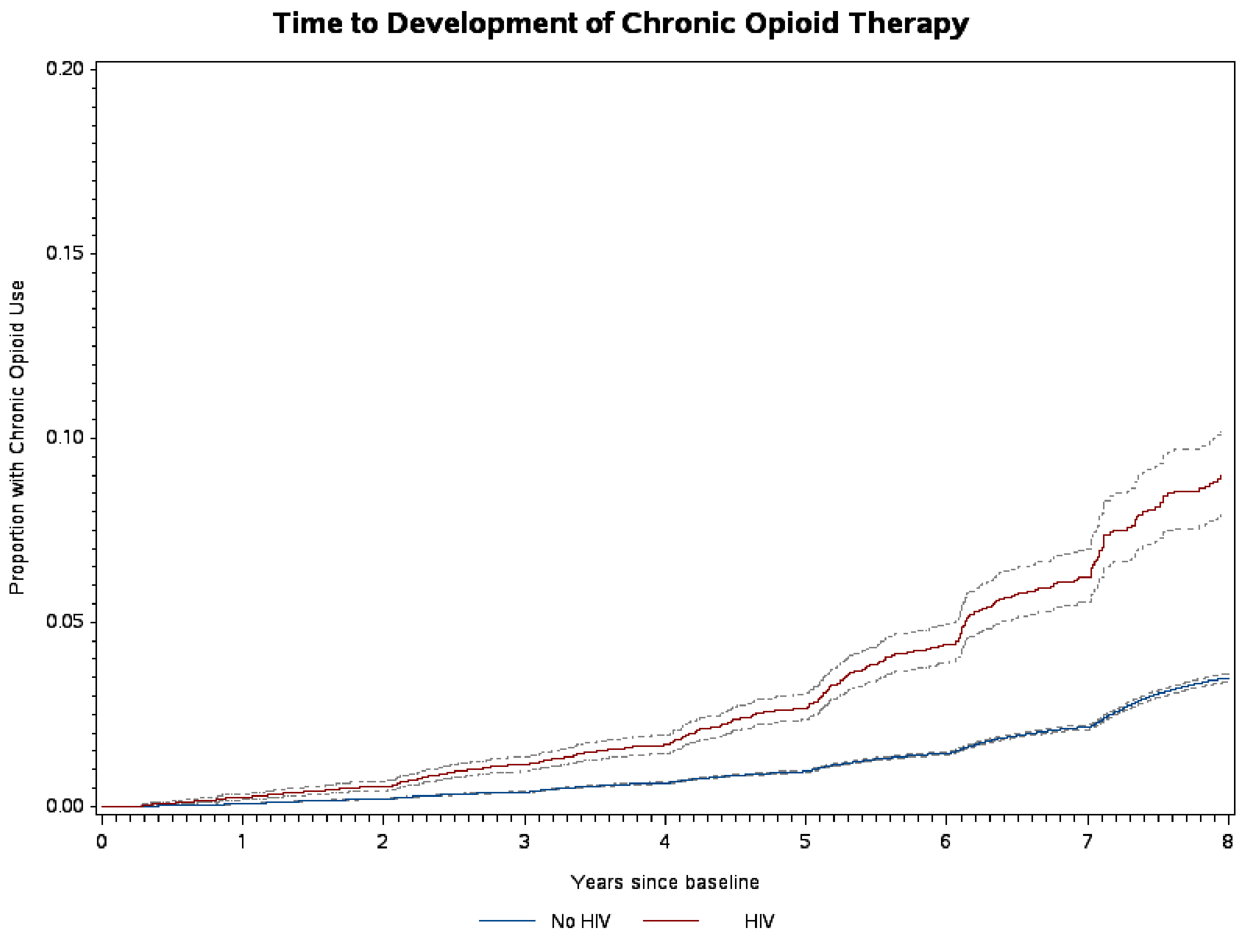
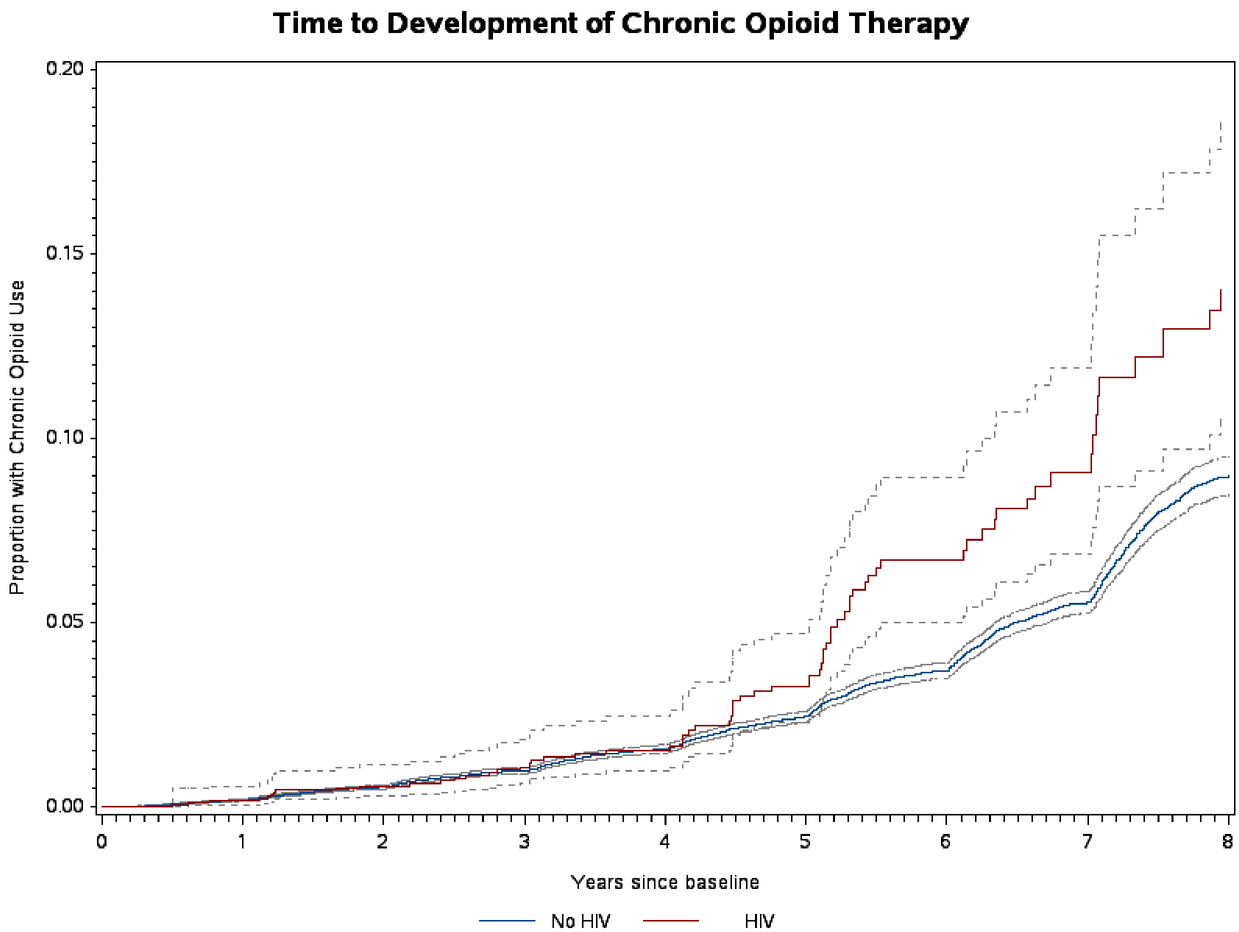


Figure 10: Kaplan-Meier estimate for the incidence of chronic opioid therapy among diabetics, weighted

Cumulative incidence of the development of chronic opioid therapy (COT) among a sample of opioid-naïve diabetics followed from January 1, 2002 until the first day of COT (defined as the 90th day of consecutive opioid use), Medicaid dis-enrollment, or December 31, 2009, weighted by inverse probability of censoring.



Supplementary Table 1: Summary of pre-defined NDCs used to identify opioid and non-opioid analgesics

Number of unique NDCs used to define each category of analgesic. Actual NDCs not listed.

Opioid Analgesics

Drug Type	Total number of NDCs included
Hydrocodone	4354
Codeine	1849
Oxycodone SA	1466
Propoxyphene	1385
Tramadol	1094
Morphine LA	681
Morphine SA	618
Hydromorphone	456
Oxycodone LA	312
Fentanyl LA	209
Methadone	206
Fentanyl SA	144
Pentazocine	137
Oxymorphone LA	130
Meperidine	113
Buprenorphine	109
Dihydrocodeine	59
Tapentadol	44
Oxymorphone SA	36
Butorphanol	12
Opium	9
Levorphanol	8
Levomethadyl	2

Non-Opioid Analgesics: NSAIDS

Drug Type	Total number of NDCs included
Ibuprofen	3958
Aspirin	1905
Naproxen	1544
Naproxen Sodium	1039
Diclofenac Sodium	1012
Indomethacin	993
Etodolac	805
Meloxicam	658
Piroxicam	607
Nabumetone	562
Ketorolac Tromethamine	541
Aspirin/Butalbital/Caffeine	480

Ketoprofen	473
Salsalate	466
Sulindac	433
Celecoxib	412
Acetaminophen/Aspirin/Caffeine	311
Oxaprozin	308
Flurbiprofen	273
Fenoprofen Calcium	237
Meclofenamate Sodium	199
Diclofenac Potassium	176
Mefenamic Acid	66
Magnesium Salicylate	57
Flurbiprofen Sodium	15
Indomethacin Sodium	12
Acetaminophen/Caffeine/Magnesium Salicylate	6
Aspirin/Butalbital	5
Diclofenac	2
Aspirin /Phenobarbital	1

Non-Opioid Analgesics: Anti-depressants

Drug Type	Total number of NDCs included
Amitriptyline Hydrochloride	1808
Doxepin Hydrochloride	909
Venlafaxine Hydrochloride	870
Imipramine Hydrochloride	667
Desipramine Hydrochloride	497
Duloxetine Hydrochloride	317
Maprotiline Hydrochloride	150
Amoxapine	134
Clomipramine Hydrochloride	113
Trimipramine Maleate	88
Imipramine Pamoate	67
Protriptyline Hydrochloride	34
Milnacipran Hydrochloride	27
Desvenlafaxine Succinate	23
Desvenlafaxine	20
Levomilnacipran Hydrochloride	9

Non-Opioid Analgesics: Anticonvulsants

Drug Type	Total number of NDCs included
Gabapentin	1863
Topiramate	657
Carbamazepine	521
Pregabalin	462

Lamotrigine	397
Levetiracetam	392
Oxcarbazepine	362
Valproic Acid	183
Zonisamide	156
Tiagabine Hydrochloride	99
Phenytoin	74
Lacosamide	13

Non-Opioid Analgesics: Muscle relaxants

Drug Type	Total number of NDCs included
Methocarbamol	1086
Cyclobenzaprine	971
Carisoprodol	884
Tizanidine	569
Chlorzoxazone	556
Baclofen	555
Orphenadrine	482
Metaxalone	387
Dantrolene	28
Chlorphenesin	4

Supplementary Table 2: Source Population by State

	2001	2002	2003	2004	2005	2006	2007	2008	2009
AL	400,608	348,109	308,529	284,698	265,084	247,037	195,232	180,105	170,777
CA	5,391,525	4,342,118	3,353,328	2,908,202	2,516,182	2,272,904	2,075,395	1,928,935	1,823,323
CO	189,420	143,828	116,024	105,290	99,810	90,385	82,550	76,655	73,157
FL	1,236,264	890	546	550	542	517	479	450	446
GA	608,229	449,141	370,809	339,324	310,339	282,338	256,794	241,086	226,566
IL	805,222	648,861	541,168	508,632	484,525	458,480	429,051	407,705	390,183
MA	691,563	601,136	498,035	435,617	410,807	390,440	370,821	384,353	373,180
MD	317,805	267,998	231,751	200,770	179,901	160,791	141,484	133,328	134,777
NC	708,849	541,111	463,805	420,910	384,087	358,201	333,141	315,776	302,489
NY	2,126,613	1,832,076	1,474,097	1,331,368	1,235,249	1,157,112	1,084,948	1,026,384	991,261
OH	834,199	647,701	562,766	514,662	480,854	448,143	417,414	395,557	384,196
PA	858,152	716,004	619,130	570,305	524,869	492,694	461,512	442,112	424,268
TX	1,225,367	918,880	765,498	680,373	612,946	556,070	522,495	487,792	454,521
WA	462,319	370,932	295,631	267,022	242,761	218,189	198,202	181,797	172,026
Total	**15,856,135**	**11,828,785**	**9,601,117**	**8,567,723**	**7,747,956**	**7,133,301**	**6,569,518**	**6,202,035**	**5,921,170**

Supplementary Table 3: Eligible Sample by State

Eligibility criteria

- ≥18 and <65 years old
- No private supplemental insurance
- No Medicare co-insurance
- Enrolled for complete calendar year

	2001	2002	2003	2004	2005	2006	2007	2008	2009
AL	114,545	129,090	118,826	111266	99272	62824	53017	52497	50530
CA	1,680,612	1,759,371	1,384,836	1109272	962494	841458	757060	700581	657605
CO	38,127	39,236	33,329	26334	26172	22706	21169	20481	20652
FL	332,870	0	0	0	0	0	1	0	0
GA	123,383	121,879	106,268	97452	88209	76313	68428	64921	63709
IL	255,548	238,859	206,394	190761	178804	160527	148007	195614	188476
MA	265,878	243,866	181,699	166935	157453	146958	136540	130089	129114
MD	133,645	127,275	97,380	82368	71282	57965	48991	46619	52846
NC	144,107	147,440	125,934	106883	95663	90181	81878	78460	77843
NY	633,017	713,667	604,489	541429	511598	466164	424646	405124	407551
OH	242,253	253,249	224,916	207868	194513	176401	154926	153412	155236
PA	284,813	274,853	238,170	219289	206447	188253	175931	164882	160874
TX	203,779	197,693	157,143	132080	118827	105743	101038	98412	93621
WA	108,562	99,414	82,295	73274	64081	55659	47278	42701	45059
Total	**4,561,139**	**4,345,892**	**3,561,679**	**3,065,211**	**2,774,815**	**2,451,152**	**2,218,910**	**2,153,793**	**2,103,116**

Supplementary Table 4: Drug categories for non-opioid analgesics

Proportion of all prescribed non-opioid analgesics included in the analysis by drug type.

	NSAIDs	Muscle relaxants	Anticonvulsants	Anti-depressants
2001	49.00	14.11	21.63	15.26
2002	47.78	14.22	22.90	15.10
2003	46.28	14.53	24.33	14.86
2004	45.77	14.63	25.17	14.43
2005	44.59	14.90	25.58	14.93
2006	42.77	15.08	27.01	15.13
2007	41.69	14.75	28.28	15.28
2008	40.83	14.94	29.13	15.10
2009	40.48	15.32	29.31	14.88

Chapter 3: High-risk opioid use among people living with HIV

Abstract

Background. Prescription opioid use is greater among people living with HIV (PLWH), yet little is known about the prevalence of specific types of high-risk use among these individuals.

Methods. We analyzed clinical and demographic data from the HIV Research Network (HIVRN) and opioid prescribing data from Medicaid claims for non-cancer patients seeking HIV treatment at four urban clinics between 2006-2010. HIVRN patients were included in the analytic sample if they received at least one incident opioid prescription. We examined four measures of high-risk opioid use: 1) high daily dosage; 2) early refills; 3) overlapping prescriptions; and 4) multiple opioid prescribers.

Results. Of 4,553 eligible PLWH, 1,794 (39.4%) received at least one incident opioid prescription during follow-up. The sample was 62% male and 62% African American with a median age of 44.5 years. High-risk opioid use occurred among 33% of incident opioid users (high daily dosage: 12.7%; early refills: 17.9%; overlapping prescriptions: 17.1%; multiple prescribers: 21.0%). About half of the cumulative incidence of high-risk use occurred within the first year of receiving an opioid prescription. After adjusting for study site and nadir CD4, the hazard of high-risk use was greater among patients with IDU as an HIV risk factor (HR=1.54, CI 1.25-1.91), non-Hispanic whites (HR=1.44, CI 1.09-1.90),

patients age 35-45 years (HR=2.07, CI 1.45-2.94) and patients who were not virally suppressed (HR=0.80, 0.66-0.99).

Conclusions. High-risk opioid use was common among PLWH. Risk assessments and counseling on the proper use of opioids is especially important within the first year of receiving an opioid prescription.

Introduction

Opioid use and opioid misuse have increased dramatically over the past two decades[1–9]. Drug overdose is now the leading cause of accidental death in the United States, with unintentional poisoning surpassing motor vehicle accidents as the leading cause of unintentional injury deaths in 2011[10]. Nearly 60% of overdose deaths in the United States involve an opioid[1], leading to a concerted effort by care providers across the country to carefully monitor the use of prescription opioids[11–13].

Growing concern surrounding the increase of opioid use disorders has led to attempts to identify precursors to opioid misuse, with the intent of allowing health providers the opportunity to intervene before patients experience adverse consequences. Some such attempts include identifying patterns of high-risk use, such as the use of multiple of prescribers and/or pharmacies ("opioid shopping"), receiving overlapping opioid prescriptions, and high daily dosage. These use patterns have been used in both research and clinical settings to identify possible or probable opioid use disorders[9,14–20]. While it is not possible to determine whether an individual is misusing opioids based on utilization patterns alone, a large body of evidence suggests that individuals with high-risk use patterns are at higher risk of injury or death[14–18,20–24].

One particularly vulnerable population at risk for opioid use disorders is people living with HIV (PLWH). HIV-associated neuropathy and antiretroviral therapy toxicities lead to a high prevalence of chronic pain among PLWH[25–29]. In addition, the prevalence of opioid use disorders is higher among PLWH than in the general population and may increase morbidity and mortality[30–32]. In this study, we characterized utilization patterns of high-risk opioid use among PLWH and identified risk factors for high-risk opioid use.

Methods

We based our assessment of high-risk opioid use on four criteria: 1) daily dosage, 2) overlapping prescriptions, 3) multiple prescribers, and 4) early refills. These criteria have been validated in prior research as a means to identify potential misuse[14–18,20–24] and/or have been recommended by clinical experts as suggestive of high-risk opioid use. A key assumption of this analysis is that individuals who receive opioid prescriptions in patterns that meet any of these four criteria are either currently misusing opioids or are at high risk for opioid misuse. The term "high-risk use" will be used throughout this paper, as we are unable to discern whether these patterns result in abuse, addiction, dependence, and/or diversion; instead, these patterns indicate a high likelihood of current or potential opioid misuse.

Study sample

We analyzed data from two sources: Medicaid pharmaceutical claims and the HIV Research Network (HIVRN). The HIVRN contains observational, longitudinal data on cohorts of PLWH enrolled in care at both community and university-based clinics[33]. The HIVRN assembles data from its network of HIV care centers for the purposes of conducting research designed to improve accessibility, quality, and safety of healthcare services available to PLWH[33]. We used the combination of Medicaid and HIVRN data to identify patients who received opioid prescriptions, to describe their utilization patterns, and to characterize individuals meeting high-risk use criteria.

We drew the study sample from a subset of the HIVRN cohort that linked their study participants' records to the Medicaid database, allowing us to examine comprehensive pharmaceutical claims from Medicaid and clinical, behavioral, and social characteristics from HIVRN. Investigators from urban health centers in Massachusetts, Maryland, and New York initiated and executed this individual-level data linkage as follows: 6,892 patient IDs from HIVRN were sent to CMS and 6,196 of these IDs were matched to the Medicaid database based on social security numbers, representing a total of 25,788 person-years[34]. Only patients with data from both sources were eligible for inclusion in our analytic sample. Patients age 18-65 were included in the study sample if they received at least one oral analgesic prescription at any time during study follow up (January 1, 2006 to December 31, 2010). Supplementary Table 5 summarizes the NDCs used to identify opioid prescriptions.

Exclusion criteria and description of final sample

The outcome definitions for this analysis required complete capture of all prescription claims. Therefore, we excluded patient-years for which the patient was also enrolled in either Medicare or private insurance at any time during the calendar year, as claims covered by supplemental insurance do not appear in the Medicaid claims file. Further, we included patient-years in the analysis only if they were continuous. If patients had a gap-year (i.e. enrolled in one year, not the next, and re-enrolled in a subsequent year), years subsequent to the gap were excluded from the analysis.

Additionally, we excluded, on a state-by-state basis, Medicaid fee-for-service or comprehensive managed care plans if they incompletely captured prescription claims as determined by data exploration within our sample and evidence from prior literature [35]. Following an analysis of the completeness and comparability of comprehensive managed care claims versus fee-for-service claims (Supplementary Table 6), we excluded patients on fee-for-service plans in Maryland and patients on comprehensive managed care plans in

Massachusetts. Patients from any state who were classified both as "fee-for-service only" and "comprehensive managed care" within the same year or as neither fee-for-service nor comprehensive managed care were also excluded from the analysis.

Finally, we excluded patient-years for the following reasons: 1) patient was younger than 18 years or older than 65 years; 2) patient was transgender (excluded because the small sample size of <1% precluded an analysis of transgender patients); 3) patient had a non-benign cancer diagnosis (excluded to remain consistent with prior opioid studies; cancer patients are treated for pain under extenuating circumstances[28,31,36,37]); 4) patient was enrolled in Medicaid for <90 days; 5) patient resided in a state other than Massachusetts, Maryland, or New York; 6) there was a discrepancy in age (>5 years) or sex between Medicaid and HIVRN; 7) patient had >1 record or >365 eligible days for the calendar year; 8) patient was a prevalent opioid user, determined using a 6-month washout period. Figure 11 shows the number excluded for each reason.

High-risk opioid use

We based our assessment of high-risk opioid use on four criteria: 1) daily dosage, 2) overlapping prescriptions, 3) multiple prescribers, and 4) early refills. We ascertained high-risk opioid use using Medicaid pharmacy claims. We based the first outcome, high daily dosage, on a standardized measure for daily dosage: morphine milligram equivalents (MME). The daily dosage and number of days dispensed for each opioid prescription claim were used to determine the MME that a patient received each day. Recommendations vary for defining the cutoff for overuse, ranging from 80 to 200 MME [4,38]. For our purposes, we defined high-risk use as receiving a total daily dosage over 100 MME/day for at least 30 consecutive days.

We defined the second criterion for high-risk use, overlapping prescriptions, as having at least one day with more than one opioid prescription from the same Drug Enforcement Agency (DEA) class, with DEA class categorized as1) long acting, 2) short acting non-Schedule II (i.e. codeine, tramadol), or 3) short acting Schedule II (i.e. hydrocodone, oxycodone). To ensure the drugs were not overlapping due to an early refill, we required that the overlapping prescriptions were either a different dosage or a different drug.

Each Medicaid prescription claim includes a unique identification number for the prescribing physician. We used this information to identify individuals who sought opioids from multiple providers within a 90-day period. All individuals who received an opioid prescription at least three distinct prescribers within a 90-day period were considered high-risk opioid users by our third criterion.

The timing of the opioid prescription refill defined the final criterion for high-risk opioid use. All prescription claims include the duration of the supply (i.e. 30-day supply) and the date that the prescription was filled. We calculated the number days early an individual filled a prescription and defined refill pickups as early if the individual refilled their prescription when at least 25% of the existing prescription remained.

We examined modified definitions in the sensitivity analyses discussed below.

Explanatory variables

Exposures of interest were collected as part of the HIVRN study protocol, through medical record chart abstraction (age, sex, race, and study site) or site-specific lab uploads processed by HIVRN (nadir CD4 and HIV RNA). We defined baseline viral suppression as

HIV RNA <200 copies/ml, determined using the closest available HIV RNA measurement within one year of baseline.

We identified comorbidities (and one exclusion criterion) using diagnosis codes from the HIVRN database. Diagnoses of interest included: depression[39] and chronic pain[40], as these are diagnoses found to be associated with high-risk opioid use in prior literature and cancer, as this was an exclusion criterion[28,31,36,37]. We assessed cancer at any point during follow-up, while we assessed depression and chronic pain prior to study baseline (i.e. prior to the patient's first opioid prescription).

Patients were considered to have cancer, and therefore excluded from the analysis, if they had two or more claims with ICD-9 codes for a non-benign cancer diagnosis listed in Supplementary Table 7. The case definition for depression was informed by a 2014 systematic review[39]; the final definition was chosen based on a consideration of sensitivity, specificity, and the source of data available (ICD-9 codes only). For the purposes of this analysis, patients with one or more diagnoses from the list of "depression" diagnosis codes in Supplementary Table 7 were considered to have depression. This algorithm has a sensitivity of 32.9% and a specificity of 99.5%. The definition for chronic pain was motivated by a 2013 paper by Tian et al.[40]. Any patient with at least one diagnosis from the list of comprehensive pain diagnosis in Supplementary Table 7 was considered to have chronic pain.

Current illicit drug use was not captured directly in either the Medicaid claims or the HIVRN data. As a surrogate marker for illicit drug use, we examined HIV acquisition risk factor to identify patients with a history of injection drug use (IDU). We classified patients with an HIV risk factor of "injection drug use", as recorded in the HIVRN database, as having a history of illicit drug use (we classified patients with multiple HIV risk factors as IDU if one of the recorded risk factors was "injection drug use").

Statistical methods

Our primary outcomes were: 1) binary indicator variables for each of the four definitions of high-risk opioid use and 2) a composite binary indicator variable for any high-risk opioid use pattern. Given that the four definitions of high-risk opioid use are not mutually exclusive, we first assessed the proportion of patients who ever experienced each of the four high-risk use behaviors, determined the patterns of overlap between the four behaviors, and calculated their incidence rates. Then we estimated the time to the first indication of any high-risk opioid use and determined characteristics associated with high-risk opioid use. As sensitivity analyses, we examined recurrences of early refills and a modified definition of overlapping prescriptions. Finally, we explored the association between high-risk use and the occurrence of emergency department visits.

Time-to-event analysis

We conducted a time-to-event analysis to determine the time to any high-risk opioid use among the study sample. The primary outcome for the time-to-event analysis was a composite outcome defined as any of the four high-risk opioid use behaviors. The time origin for each individual was the date of the first opioid prescription, and the endpoint of interest was the first date at which there was evidence for high-risk opioid use. Patients were censored on the first of either: 1) date of death, 2) last day of Medicaid coverage, or 3) December 31, 2010.

We estimated the incidence rate and median time to first occurrence of high-risk opioid use. Then, because the time-to-event analysis followed patients only until their first high-risk use behavior, we also examined incidence rate of subsequent high-risk use behaviors. Finally, we fit a Cox proportional hazards model to estimate the association between high-risk use and our hypothesized risk factors, including IDU, depression, chronic pain, age, sex, race, nadir CD4, and baseline HIV viral suppression.

Sensitivity analyses

Unlike the indicators for multiple prescribers and overlapping prescriptions, which both require, by definition, the occurrence of a behavior more than once, the early refills indicator does not incorporate recurrence into its case definition. Therefore, as a sensitivity analysis, we calculated the proportion of patients who sought early refills repeatedly and estimated the time to first event, time to second event, and time to third event. Among those with at least one early refill, we estimated the difference in 1-year restricted mean survival times to describe the time between first and second events and the time between the second and third events.

To evaluate the potential impact of misclassifying high-risk use in the scenario where a single provider prescribed multiple prescriptions to identify the correct dosage for an opioid-naïve patient, we conducted a sensitivity analysis whereby the overlapping prescriptions criterion was met only if distinct providers wrote the prescriptions. We used the revised definition to re-calculate the incidence rate of overlapping prescriptions and to re-define the composite outcome used in the survival analysis.

Association with emergency department visits

To explore consequences of high-risk opioid use, we examined the association between high-risk opioid use and emergency department visits. This exploratory analysis was based on the assumption that non-opioid related emergency department visits were approximately equal at baseline between patients with high-risk opioid use and those without high-risk use. Under this assumption, an increase in emergency department visits among patients with high-risk opioid use could be attributed to their opioid use.

We modeled the number of emergency department visits per year longitudinally using a generalized linear model with a Poisson distribution, fit using generalized estimating equations with an autoregressive correlation structure to account for within-patient correlation. We included a time-varying covariate for the presence of any high-risk opioid use behavior. Because emergency department visits were measured annually (total number per year, no dates specified), we could not precisely determine whether the visit occurred before or after the onset of the high-risk utilization behavior. As a best estimate, we attributed high-risk use behaviors within the first half of the year to emergency departments within that year; high-risk use behaviors in the second half of the year were attributed to emergency department visits in the next year.

Results

Our sample included 1,794 PLWH with at least one incident opioid prescription between 2006-2010, which represents 39.4% of the 4,553 patients meeting the eligibility criteria (31.4% of eligible patients did not receive any opioid prescriptions during follow-up and 29.2% were prevalent opioid users). The final analytic sample was 61.7% male and the median age at study baseline was 44.5 years (interquartile range 38-50 years). Nearly two-thirds (62.0%) were African American. Approximately one third (31.3%) of patients had an HIV acquisition risk factor of IDU, 31.1% had a diagnosis of depression prior to baseline, and 19.3% had a diagnosis of chronic pain prior to baseline. Most patients were from New York (62.8%) and Maryland (30.8%), while 6.5% were from Massachusetts (Table 9).

Among the 1,794 patients who received at least one incident opioid prescription, the median number of opioid prescriptions per patient per year was 2 (IQR: 1-6). The median daily dosage was 39.3 MME (IQR: 22.5-80; mean: 71.1). Slightly more than half of all opioid prescriptions (54.9%) were short-acting Schedule II, 23.2% were long acting, and 21.9% were short-acting non-schedule II. The most commonly prescribed opioid was short-acting oxycodone (43.5% of all prescription opioids) (Table 9).

Incidence of high-risk use

Approximately one third (32.8%) of patients ever met one of the four high-risk use criteria. The most common high-risk use behavior was multiple prescribers, with 21.0% of patients ever receiving opioid prescriptions from at least 3 distinct prescribers in 90 days, for an incidence rate (IR) of 10.7 per 100 person-years (PY). Eighteen percent of patients ever refilled a prescription when at least 25% of the prior prescription remained (IR=9.1 per 100 PY); 17.1% ever had overlapping prescriptions (IR=8.6 per 100 PY); and 12.7% ever had a high daily dosage over 100 MME for 30 or more consecutive days (IR=6.1 per 100 PY) (Table 10).

Figure 12 depicts the overlap between the four use patterns, showing that 75 (4.2%) patients met criteria for all four high-risk behaviors while 1,205 (67.2%) did not meet criteria for any behavior. 232 (12.9%), 145 (8.1%) and 137 (7.6%) met criteria for one, two and three outcomes, respectively.

Of the 589 individuals who met high-risk use criteria, 357 met criteria for more than one high-risk use pattern. Table 11 depicts incidence rates of subsequent high-risk patterns among individuals who fulfilled multiple criteria for high-risk use. For example, among 95 patients who first met criteria for high daily dosage, the incidence rate of subsequently meeting criteria for another pattern ranged from 16.1 per 100 PY (overlapping prescriptions) to 25.1 per 100 PY (multiple prescribers).

Time-to-event analysis

The incidence rate for any high-risk opioid use behavior was 20.0 events per 100 person-years. After 1 year of follow-up, the cumulative incidence was 26% and at 4 years of follow-up the cumulative incidence was 45%. Figure 13 displays the cumulative incidence function for the composite high-risk opioid use outcome; the solid curve shows the total cumulative incidence of any high-risk use and the dashed lines depict the cumulative incidence that each of the four high-risk use patterns contribute individually.

Patients with complete covariate data (n=1,412) were included in the multivariable regression analysis, representing 422 events. The 382 patients with missing data were excluded due to missing HIV viral load or CD4 measurements; the incidence rate of high-risk opioid use was not differential among patients excluded due to missing lab values. In a multivariable adjusted Cox regression model, IDU as an HIV acquisition risk factor, age, race, and baseline viral suppression were associated with high-risk opioid use (Table 12).

The adjusted hazard ratio (aHR) for high-risk opioid use was 1.54 (95% CI 1.25-1.91) comparing patients with IDU as an HIV acquisition risk factor to those with a non-IDU related risk factor (i.e. men who have sex with men, high-risk heterosexuals). Patients who were age 35-45 at study baseline had twice the hazard for high-risk use compared to patients less than 35 at study baseline (aHR=2.07, 95% CI 1.45-2.94). Patients older than 45 also had an increased hazard for high-risk use compared to patients in the lowest age category, but the increased hazard decreased with each increasing age category (aHR=1.88, 95% CI 1.31-2.69 for patients age 45-55 at baseline; aHR=1.44, 95% CI 0.92-2.26 for patients age 55-65 at baseline).

Patients who were virally suppressed showed a significantly lower hazard for high-risk opioid use (aHR=0.80, 95% CI 0.66-0.99). Non-Hispanic whites had a higher risk for high-risk opioid use compared to African Americans (aHR=1.44, 95% CI 1.09-1.90), while Hispanics and patients of unknown or other races demonstrated a non-significant decreased hazard for high-risk opioid use compared to African Americans.

Non-significant associations were found with respect to sex and chronic pain. Males demonstrated a non-significant increased hazard of high-risk opioid use (aHR=1.18, 95% CI 0.97-1.45). Having a diagnosis chronic pain prior to one's first opioid prescription was associated with a non-significant increased hazard for high-risk opioid use (aHR=1.17, 95% CI 0.92-1.50).

Recurrence of early refills: a sensitivity analysis

Among patients who met early refill criteria (n=322), the mean number of early refills over the follow-up period was 2.7 (median 2, IQR 1-3). In total, 150 patients (8.4%) refilled their opioid prescription only once, 59 (3.3%) refilled early exactly twice, 41 (2.3%) refilled early exactly three times, and 72 (4.0%) refilled early four or more times, up to a maximum of 17 times over the duration of follow-up. The incidence rates for first early refill, second early refill, and third early refills were 9.1 per 100 person-years, 4.5 per 100 person-years, and 2.8 per 100 person-years, respectively. The top panel of Figure 14 displays the Kaplan-Meier survival curves for time to first, second, and third early refill. The bottom panel of Figure 14 shows the time from the first (or second) early refill until the subsequent (either second or third) early refill.

Among the full sample of 1,794 patients, the restricted mean survival time (RMST) up to 4.8 years of follow-up for the first early refill was 3.9 years (95% CI 3.8-4.0 years) and the RMST up to one year of follow-up was 0.73 years (95% CI 0.70-0.76 years). That is, the expected time to early refill is 0.73 years during the first year of follow-up. When examining the time between the first and second early refills, the RMST up to one year was 0.41 years (95% CI 0.36-0.46 years). Therefore, comparing the RMST for first as compared to second early refill over a 1-year period, it took patients about 0.32 years (or 16.6 weeks) longer to reach their first early refill than their second. The comparable 1-year RMST for the time to third early refill following the date of the second early refill was 0.36 years (95% CI 0.30-0.42 years).

Overlapping prescriptions: a sensitivity analysis

When we redefined overlapping prescriptions such that the overlapping prescription criteria was only satisfied when distinct prescribers provide the prescriptions, the incidence rate dropped to 7.1 per 100 person years (from 8.6 per 100 person-years). When restricting the definition further, requiring the overlapping prescriptions not only to come from distinct providers but also to be distinct drugs, the incidence rate decreased to 5.7 per 100 person-years. Because overlapping prescriptions only occasionally defined the endpoint of interest in the composite outcome survival analysis, the overall incidence rate for high-risk opioid use remained fairly unchanged: the modified definitions of overlapping prescriptions reduced the incidence rate for high-risk opioid use from 20.0 per 100 person-years to 19.7 and 19.1 per 100 person-years, respectively.

Association with emergency department visits

Emergency department visits were generally infrequent, with a mean number of emergency department visits per year of 0.71 (median=0 and IQR=0-1). In a Poisson model adjusted for age, sex, race, injection drug use, nadir CD4, and baseline viral suppression, we found a slight increase in emergency department visits among patients with high-risk opioid utilization compared to those without, but this increase was not statistically significant (aRR=1.20, 95% CI 0.98-1.50).

Discussion

We conducted time-to-event analysis among PLWH receiving an incident opioid prescription to estimate the incidence of high-risk opioid use and determine factors associated with high-risk use. High-risk opioid use was common among these subjects, with 33% of patients exhibiting at least one of the four high-risk use outcomes. Of the four high-risk use metrics we studied, the incidence rate was highest for multiple prescribers, followed by early refills and then overlapping prescriptions. These results are important because while chronic non-cancer pain is common among PLWH, relatively little is known regarding patterns of high-risk opioid use among this population. Our findings underscore the importance of prescription drug monitoring programs to track prescribing patterns, including prescriptions dispensed by other providers.

The four distinct high-risk use patterns do not occur in isolation. Prior literature has demonstrated an association between each of these four high-risk use behaviors independently and adverse consequences such as opioid use disorders or opioid diversion[14–18,20–23], but few studies have compared the validity of the metrics to one another. Though the goal of this paper was not to directly compare the four distinct high-risk use patterns, we did find that the incidence rate of each pattern increased substantially if an individual had already met criteria for one of the other high-risk use patterns, suggesting that these behaviors are interrelated.

Of note, approximately half of the total cumulative incidence of high-risk use occurred within the first year after a patient received an incident opioid prescription. The first year of opioid use likely represents a critical period, as addiction and development of opioid use disorders often occur early in treatment[41]. Because of the startling incidence of high-risk opioid use within the first year, it is especially important for providers to ensure careful and dedicated opioid counseling to patients receiving new opioid prescriptions. Opioid risk assessment screenings such as the Brief Risk Interview, which has been found effective in predicting aberrant opioid use[42], may be useful among high-risk populations.

Similar to research in HIV-negative populations, we found a higher hazard for high-risk opioid use among patients with a history of IDU. We also found an increased hazard for high-risk opioid use among patients age 35-55 years (but not 55-65) compared to patients age 18-35, among men compared to women, and among non-Hispanic whites compared to African Americans. Interestingly, we did not find an association between depression and high-risk opioid use, which is in contrast to previous literature[17,18,43,44]. The use of ICD-9 diagnostic codes to define depression may have been an imperfect identifier, as psychiatric conditions that were undiagnosed and/or did not appear in ICD-9 claims could not be examined.

Approximately half of all patients with at least one early refill had recurrent early refills. Over a one-year period, patients who had at least one early refill spent an average of 0.73 years (approximately 38 weeks) before seeking their first early refill. The one-year RMST between the first and second refill was slightly shorter (approximately 21 weeks), and the one-year RMST between the second and third early refills decreased even more to approximately 19 weeks. This pattern indicates that while early refills become habitual among only some patients, those who engage in early refill behavior numerous times may be of particular concern.

Modifying the definition of overlapping prescriptions to exclude overlapping prescriptions that were prescribed by the same provider reduced the incidence rate by nearly 20%. While the revised definition did not impact the incidence of the composite high-risk use outcome, investigators should be cautious when using overlapping prescriptions to flag possible or probable misuse; overlapping prescriptions, especially if they are prescribed to opioid-naïve patients by a single provider, may be an artifact of dose titration rather than opioid misuse.

We chose to use a sensitive definition for overlapping prescriptions by requiring only a one-day overlap. More stringent criteria could be used; however, we found that 90% of patients who had an overlap of at least one day also had an overlap of at least 4 days, with a median number of overlapping days of 36. Therefore, we used the conservative definition for overlapping prescriptions to ensure capture of all instances of overlapping prescriptions. Even with our sensitive definition, overlapping prescriptions was only the third most common of the four behaviors examined.

High-risk opioid use is a difficult behavior to measure, as the level of opioid consumption that is inappropriate may vary by individual. Our assessment of high-risk use from prescription claims therefore acted as a proxy for misuse, which is not a perfect surrogate. We estimated the association between combinations of the high-risk utilization metrics and change in annual emergency department visits to assess face validity of the measures but found no significant associations. The null findings are likely due to the non-specific nature and relative rarity of emergency department visits. Outcomes more directly related to high-risk opioid use, such as cause-specific mortality, overdose events, or incident opioid dependence and/or addiction diagnoses, would provide a more optimal means for validation.

Because we defined the outcome for this study using prescription claims records as a surrogate marker for opioid misuse, the increased hazard for high-risk use could be due in part to patients having more severe pain or receiving treatment from providers who tend to prescribe more opioids, thereby increasing the likelihood of meeting high-risk use criteria. One must be cautious in interpreting these results: we identified patients at highest risk for obtaining opioid prescriptions in patterns that are predictive of high-risk use, not necessarily patients who are currently misusing opioids.

Our study had some limitations. We were unable to determine whether patients seeking opioid from multiple prescribers did so from two or more providers within the same clinic, a pattern that may reflect a trend in practice patterns within a clinic rather than a patient's high-risk use behavior. Because we analyzed claims data, we only know whether drugs were dispensed, but not if or how the patient took the drug. Similarly, we were unable to study adverse consequences of high-risk opioid use such as addiction, overdose, or diversion. Analyzing data only from patients who were enrolled in Medicaid restricted the generalizability of the study; however, Medicaid is the largest insurer of PLWH, covering approximately 40% of nonelderly PLWH in care[45]. Finally, we analyzed prescriptions claims from 2006-2010, which represents an era slightly before widespread adoption of recent opioid prescribing recommendations.

Despite these limitations, our study had several strengths. The combination of two distinct data sources allowed us to address some challenges of using Medicaid data alone, including the inability of studies using claims data to examine clinical outcomes (i.e. CD4 and HIV RNA lab values) and demographic data that are often missing and/or inaccurate in claims data (i.e. race/ethnicity). Additionally, the four distinct study sites allowed us to examine utilization practices that may vary by location; the addition of even more study sites could add further value to future research. Finally, the analysis of the overlap between four distinct utilization behaviors provided further insight into patterns of opioid use that are most predictive of harmful outcomes.

This study extends existing knowledge about characteristics associated with high-risk opioid use to PLWH and expands on prior studies examining utilization patterns indicative of opioid misuse. We simultaneously analyzed previously described metrics for doctor shopping, overlapping prescriptions, high daily dosage, and early refills to determine the incidence rates of the behaviors both separately and combined. Finally, we described characteristics associated with high-risk use among PLWH. Our results can be used to help identify patients who may benefit most from additional opioid screening and counseling.

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Table 9: Descriptive statistics

N=1,794 patients receiving at least one incident opioid prescription	
Patient Characteristics, N (%)	
Age at baseline, *median (IQR)*	44.5 (38.2, 50.1)
Sex	
Male	1,107 (61.7)
Female	687 (38.3)
Race	
African American	1,113 (62.0)
White, not Hispanic	268 (14.9)
Hispanic	397 (22.1)
Unknown/Other	16 (0.9)
State	
Maryland	552 (30.8)
Massachusetts	116 (6.5)
New York	1,126 (62.8)
IDU as HIV risk factor	561 (31.3)
Depression prior to baseline	558 (31.1)
Chronic pain prior to baseline	346 (19.3)
Nadir CD4, *median (IQR)*	281 (130, 447)
Virally suppressed at baseline	572 (40.4)
Duration of follow-up in years, *median (IQR)*	2.2 (1.1, 3.5)
Total person-years of follow-up	4,120.34
Died during follow-up	143 (8.0)
Prescription Characteristics, N (%)	
Total number of opioid prescriptions	17,896
Annual opioid prescriptions per person, *median (IQR)*	2 (1, 6)
Daily dosage in morphine milligram equivalents, *median (IQR)*	39.3 (22.5, 80)
Drug Enforcement Agency Class	
Long acting	4,154 (23.2)
Short acting non-Schedule II	3,910 (21.9)
Short acting Schedule II	9,832 (54.9)

Table 10: Summary statistics for each high-risk use behavior

N=1,794 patients receiving at least one incident opioid prescription

	Number (%) of individuals	Incidence rate per 100 person-years
High daily dosage	228 (12.7)	6.1
Early refills	322 (17.9)	9.1
Overlapping prescriptions	307 (17.1)	8.6
Multiple prescribers	376 (21.0)	10.7

Table 11: Incidence rate of subsequent high-risk opioid use patterns among patients who met multiple criteria for high-risk use, by first-occurring high-risk use pattern

N=589 patients with at least one high-risk use event

		Incidence Rate (per 100 person-years) of Additional High-risk Use Patterns following First Occurrence of High-Risk Use			
		High daily dosage N=133	Early refills N=166	Overlapping prescriptions N=180	Multiple prescribers N=165
First Occurring High-Risk Use Pattern	High daily dosage (N=95)	--	21.6	16.1	25.1
	Early refills (N=156)	18.5	--	48.1	39.2
	Overlapping prescriptions (N=127)	30.0	30.8	--	38.9
	Multiple prescribers (N=211)	10.0	27.5	25.3	--

Table 12: Multivariable adjusted Cox regression model for time to first high-risk opioid use behavior

N=1,412 patients with complete covariate data; 448 events; model adjusted for study site

	HR (95% CI)	p-value
Age		
18 to <35	Ref	
35 to <45	2.07 (1.45-2.94)	<0.001
45 to <55	1.88 (1.31-2.69)	0.001
55 to <65	1.44 (0.92-2.26)	0.110
Male Sex	1.18 (0.97-1.45)	0.100
Race		
African American	Ref	
White, not Hispanic	1.44 (1.09-1.90)	0.010
Hispanic	0.87 (0.67-1.13)	0.309
Unknown/Other	0.77 (0.24-2.42)	0.651
IDU as HIV risk factor	1.54 (1.25-1.91)	<0.001
Depression diagnosis	1.01 (0.82-1.25)	0.896
Chronic pain diagnosis	1.17 (0.92-1.49)	0.192
Nadir CD4		
<50	Ref	
50 to <200	1.26 (0.90-1.76)	0.173
200 to <350	1.03 (0.76-1.38)	0.867
350 to <500	0.88 (0.65-1.18)	0.381
≥500	0.99 (0.72-1.37)	0.967
Baseline HIV viral suppression (<200)	0.80 (0.66-0.99)	0.036

Figure 11: Flow diagram

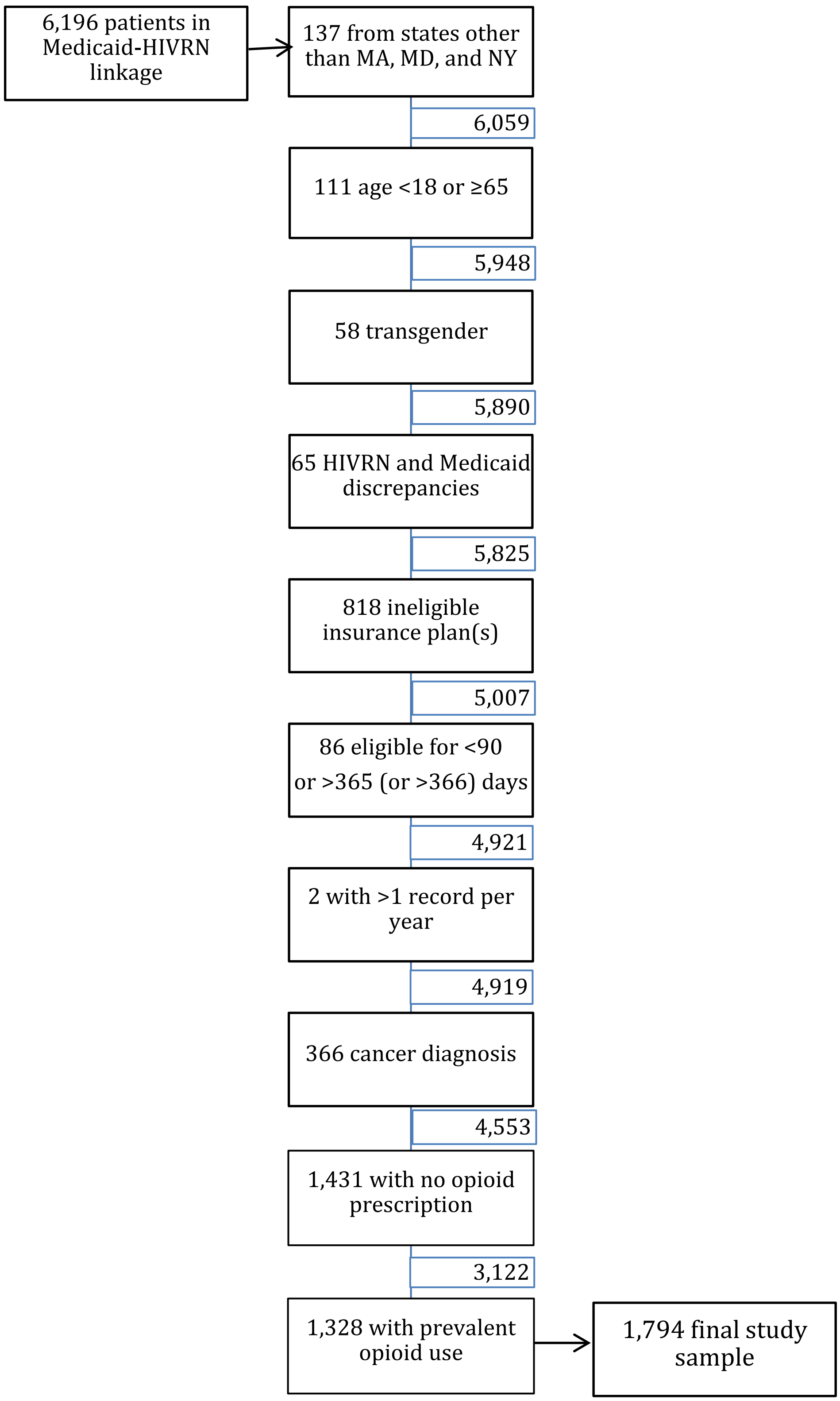


Figure 12: Venn diagram

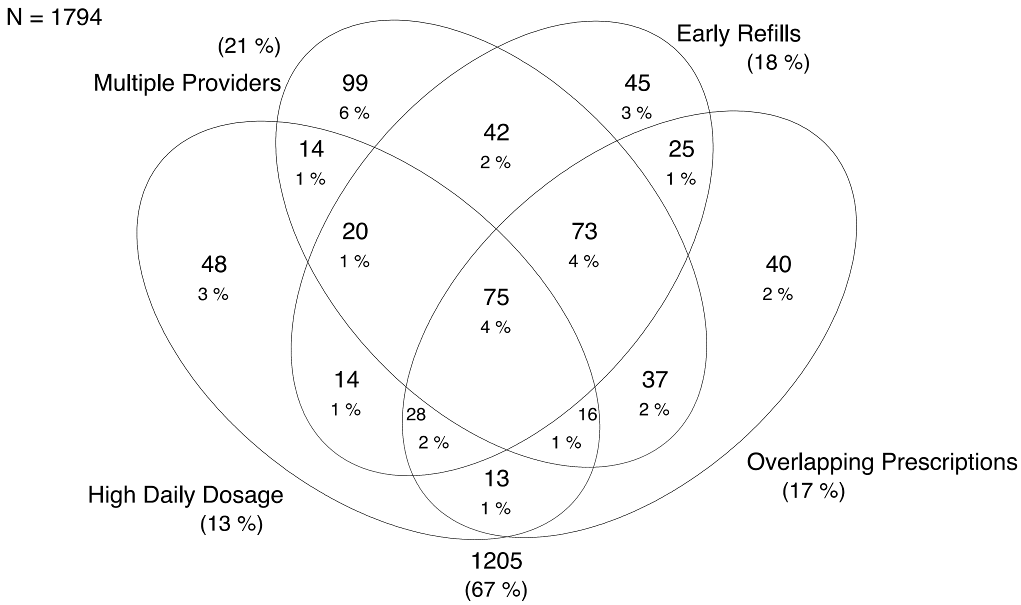


Figure 13: Cumulative incidence of high-risk opioid use

The solid curve (the sum of Regions A through D) depicts the total cumulative incidence of any high-risk use behavior. The dashed lines depict the portion of the total cumulative incidence that each of the four high-risk use patterns contributes. Region A depicts the cumulative incidence contributed by high-daily dosage. Region B depicts the cumulative incidence contributed by overlapping prescriptions. Region C depicts the cumulative incidence contributed by early refills. Region D depicts the cumulative incidence contributed by multiple providers.

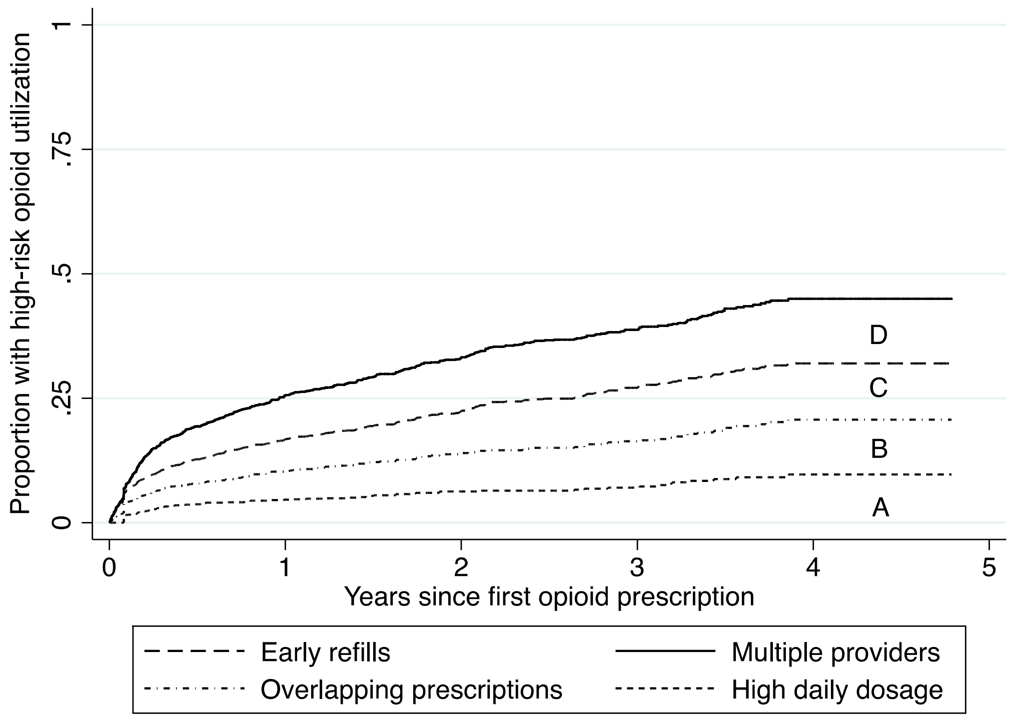
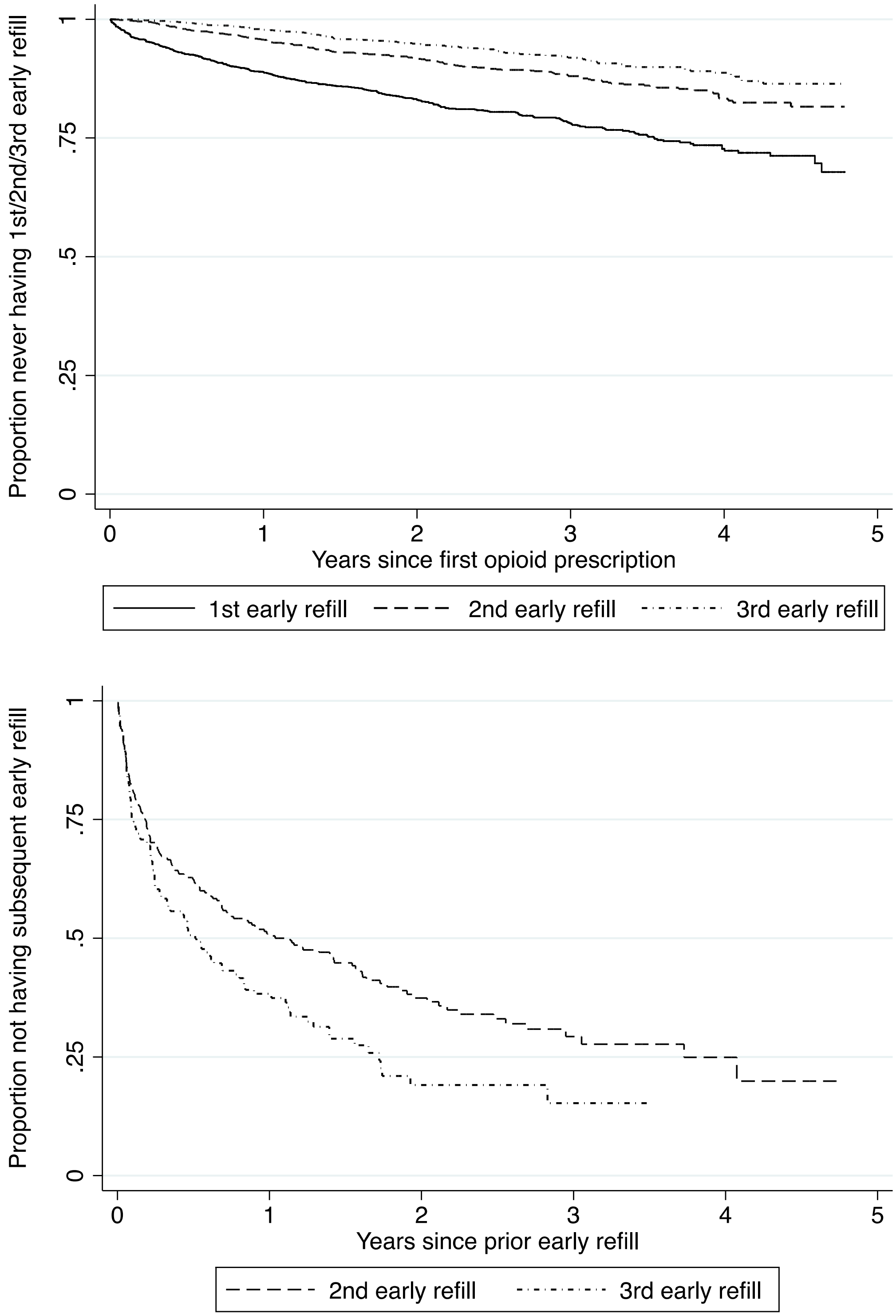


Figure 14: Time to recurrent early refills



Supplementary Table 5: Summary of pre-defined NDCs used to identify opioid analgesics

Number of unique NDCs used to define opioid analgesics. Actual NDCs not listed.

Drug Type	Total number of NDCs included
Hydrocodone	4354
Codeine	1849
Oxycodone SA	1466
Propoxyphene	1385
Tramadol	1094
Morphine LA	681
Morphine SA	618
Hydromorphone	456
Oxycodone LA	312
Fentanyl LA	209
Methadone	206
Fentanyl SA	144
Pentazocine	137
Oxymorphone LA	130
Meperidine	113
Buprenorphine	109
Dihydrocodeine	59
Tapentadol	44
Oxymorphone SA	36
Butorphanol	12
Opium	9
Levorphanol	8
Levomethadyl	2

Supplementary Table 6: Exploration of two types of Medicaid plans

	Patients with ≥1 prescription (any)	Patients with ≥1 opioid prescription
Fee-for-service plans (N=3,344)		
State of residence		
Massachusetts (n=422)	407 (96.4)	228 (54.0)
Maryland (n=283)	192 (67.8)	106 (37.5)
New York (n=2,629)	2,578 (97.7)	1,805 (68.4)
Mean prescriptions per person per year		
Massachusetts	45.5	6.1
Maryland	67.3	10.5
New York	76.0	7.2
Median prescriptions per person per year (IQR)		
Massachusetts	36 (15, 61)	2 (1, 7)
Maryland	46 (14, 103)	4 (2, 12.5)
New York	66 (34, 107)	5 (2, 12)
Comprehensive managed care plans (N=3,133)		
State of residence		
Massachusetts (n=52)	40 (76.9)	17 (32.7)
Maryland (n=1,542)	1,496 (97.0)	1,092 (70.8)
New York (n=1,539)	1,497 (97.3)	864 (56.1)
Mean prescriptions per person		
Massachusetts	34.6	6.2
Maryland	51.9	7.2
New York	65.9	6.2
Median prescriptions per person per year (IQR)		
Massachusetts	20.5 (10, 38.5)	5 (1, 9)
Maryland	41 (16, 75)	3 (1, 10)
New York	52 (23, 95)	3 (1, 11)

Supplementary Table 7: Exposure definitions

Diagnosis	ICD-9 Codes used for Case Definition
Cancer	140-239
Depression	296.20 296.21 296.22 296.23 296.24 296.25 296.30 296.31 296.32 296.33 296.34 296.35 300.4 311 296.5 296.6 296.82 296.90 309.0 309.1 309.28
Chronic pain	338.2 338.21 338.22 338.28 338.29 338.4 307.8 307.89 338 719.41 719.49 719.45 719.46 719.47 720 720.2 720.9 721 721.1 721.2 721.3 721.41 721.42 721.6 721.8 721.9 721.91 722 722.1 722.11 722.2 722.3 722.31 722.32 722.39 722.4 722.51 722.52 722.6 722.7 722.71 722.73 722.8 722.81 722.82 722.83 722.9 722.91 722.92 722.93 723 723.1 723.3 723.4 723.5 723.6 723.7 723.8 723.9 724 724.01 724.02 724.09 724.1 724.2 724.3 724.4 724.5 724.6 724.7 724.79 724.8 724.9 729 729.1 729.2 729.4 729.5

Chapter 4: Estimating the prevalence of opioid diversion using an indirect questioning technique

Abstract

Background. The prevalence of opioid diversion is difficult to measure because of social desirability bias and because of this there is a dearth of information on diversion. Given the increased prevalence of opioid use among people living with HIV (PLWH), the risk for opioid diversion is concerning in this population. We applied a method designed to provide a more accurate estimate of sensitive behaviors to assess the prevalence of opioid diversion among PLWH.

Methods. Between October of 2016 and June of 2017, we randomized patients from the Johns Hopkins HIV Clinical Cohort who had ever received an opioid prescription to answer either a direct or indirect question about opioid diversion. For the indirect question, we applied the crosswise method. We estimated the prevalence of opioid diversion under each method. We further estimated the prevalence of opioid diversion in subsets of the sample by sex, race/ethnicity, HIV risk group, illicit drug use, smoking status, depressive symptoms, and anxiety.

Results. Of 1,158 patients screened, 541 (46.7%) reported that they had ever received an opioid prescription. Among these patients, 284 answered the indirect question about opioid diversion and 244 directly answered whether they had ever diverted opioids. The prevalence of opioid diversion using the indirect questioning method was 11.5% (95% CI

6.4%-16.6%) and the prevalence using the direct questioning method was 6.1% (95% CI 3.5%-9.9%). Ever having used cocaine was associated with an increased prevalence of opioid diversion (aOR=16.3).

Conclusions. The crosswise method of indirect questioning can be used to estimate the prevalence of opioid diversion in the absence of social desirability bias. Among our sample of people living with HIV, the prevalence of opioid diversion was nearly twice as high using the indirect questioning method compared to a direct questioning method.

Introduction

Rates of opioid prescriptions have risen over the past two decades, leading to an increase in aberrant opioid use, drug overdose, and drug-related mortality[1]. Initiatives such as the development of prescription drug monitoring programs are designed to reduce overprescribing and prevent individuals from receiving too many opioids[2]. Nonetheless, a large supply of opioid prescriptions is still in circulation across the United States[3]. The dispensing of excess or unneeded opioid prescriptions opens the door for intentional or unintentional opioid diversion, or the unlawful transfer of an opioid prescription to an unintended recipient.

Opioid diversion is particularly dangerous because it results in unmonitored consumption of the drugs. The National Survey on Drug Use and Health found that over 70% of individuals who abuse prescription painkillers received the drugs through diversion[4]. Despite the high prevalence and severe negative consequences of opioid diversion, efforts to combat diversion in the United States have been inconsistent and largely ineffective[4], leading to a continued problem with opioid diversion across the country.

Accurate prevalence estimates for aberrant opioid use are difficult to obtain, as individuals hesitate to self-report behaviors such as opioid overuse or diversion that are stigmatized or illegal. An indirect method for estimating the prevalence of opioid misuse can provide a more accurate prevalence measurement and can be used to validate direct estimation methods. With an indirect questioning method, researchers induce a known amount of measurement error into the study design, which provides anonymity to the respondent and increases the likelihood of honest responses. This measurement error can subsequently be adjusted to obtain accurate estimates for the prevalence of sensitive behaviors.

In this study, we applied an indirect questioning technique to measure the prevalence of opioid diversion in the Johns Hopkins HIV Clinical Cohort (JHHCC). Indirect questioning techniques have been found to elicit more honest responses, as individuals are not asked to provide an answer to a sensitive question directly. We used the crosswise method of indirect questioning[5] to estimate the prevalence of opioid diversion in the study population, compared the prevalence estimated through indirect questioning to the prevalence estimated by directly asking patients about opioid diversion, and used logistic regression techniques for randomized responses to identify risk factors for diversion using the outcome as identified through indirect questioning.

Methods

The JHHCC contains data on approximately 2,000 HIV-infected patients, with approximately 85% of them seeking all of their care within the Johns Hopkins system[6]. As part of the standard of care at the clinic, patients are asked to consent to participate in the clinical cohort. Consenting patients complete an automated computer-assisted self-interview (ACASI) survey at all study visits. An ACASI is a computerized interview that the patient completes in private, without having to verbally disclose information directly to the provider. Prior research suggests that the use of ACASI software may produce more accurate self-reported information on sensitive subjects compared to a verbal interview[7]. All patients who provided informed consent to enter the clinical cohort were eligible to answer the opioid diversion questions on the ACASI. Following Institutional Review Board

(IRB) approval from the Johns Hopkins School of Medicine IRB, we collected data between October 2016 and June 2017.

We began by asking a screening question to all patients: "Has your doctor ever given you a prescription narcotic such as oxycontin, oxycodone, Percocet, fentanyl, tramadol, etc. to treat pain?" If the patient answered no to this question, we did not provide any further questions about opioid diversion. Patients who answered yes to the screening question were randomized to answer a question about opioid diversion, either directly or indirectly. The direct question asked: "Have you ever given away or sold your prescription pain medication (such as oxycodone, Percocet, tramadol)? This includes giving the medicine to a family member or friend for free."

For the indirect question, we employed crosswise method[5]. The crosswise method is an indirect questioning technique whereby respondents simultaneously answer two true/false questions (one sensitive question and one non-sensitive question, the answers to both are unknown to the interviewer) by stating whether the answer to both questions is the same or different. The rationale behind this method is that because the respondent does not state whether the responses are true or false, the stigma associated with answering the sensitive question decreases and the respondent is more likely to provide an honest answer.

For patients randomized to the indirect question, the ACASI presented instructions to consider the answer to both the sensitive and non-sensitive question simultaneously. The non-sensitive question was "Was your mother born in February, April or November? If you do not know your mother's birthday, think of your grandmother or some other woman whose birthday you know." The non-sensitive was the same as the direct response question above. As is standard with the crosswise method for indirect questioning the response options were: A) "My response is 'No' to both questions OR 'Yes' to both questions" or B) My response is 'Yes' to one of the questions and 'No' to the other.

Because the required sample size for crosswise technique depends on the prevalence of the non-sensitive question, we chose to ask about the three months with the lowest proportion of birthdays. We chose three months because the prevalence of more than three would require too large a sample size than was feasible, and fewer than three months may be too specific for patients to feel their answers are truly anonymous. Based on historical CDC[8,9] (1950 and 1955) and UN[10] (1969-2014) data for all live births in the United States, we expected the probability of their mother being born in those three birth months to be 23.5%.

We pilot tested the questions using a convenience sample by presenting the questions to patients and asking for verbal feedback regarding the clarity of the question. A research assistant was present while patients completed the ACASI and was available to answer questions if patients expressed confusion about the technique.

Statistical Methods

This study was designed to 1) estimate the prevalence of opioid diversion in the JHHCC and 2) to identify risk factors for opioid diversion. We applied an indirect questioning technique, the crosswise method, to ask study participants about opioid diverting behavior. This technique induces a pre-determined amount of measurement error, which can be corrected using the prevalence formula described by Yu et al.[5]:

$$\hat{\pi} = \frac{\hat{\lambda} + p - 1}{2p - 1}, \text{with } p \neq 0.5,$$

where $\hat{\pi}$ is the probability of opioid diversion, p is the probability that the non-sensitive question is true, and $\hat{\lambda}$ is the proportion of respondents indicating that the answers to the sensitive and non-sensitive questions are the same. We used an estimated probability p=0.235 and measured $\hat{\lambda}$ from the sample data to calculate the estimated probability of opioid diversion in the JHHCC population.

The variance for the prevalence estimate can be calculated as follows[5]:

$$\widehat{\mathrm{Var}(\pi)} = \frac{\pi * (1 - \pi)}{n} + \frac{p * (1 - p)}{n * (2p - 1)^2}.$$

To assess factors that may be associated with opioid diversion, we calculated the prevalence of diversion within subsets of the full study sample, stratified by characteristics we hypothesized may be associated with opioid diversion, including age, sex, mental health co-morbidities, and history of illicit substance use. Because of the small sample size and correspondingly large variance within subsets of the study sample, the stratified prevalence estimates were a secondary analysis.

Finally, we used the results of indirect questioning to identify risk factors for opioid diversion using a multivariate generalized linear model designed for the analysis of randomized response outcomes. To achieve this, we used the RRreg package in R[11] and specified that the data were collected under the crosswise model. We considered demographic, social, and behavioral risk factors including age, sex, race, mental health diagnoses, HIV risk factors, smoking, and illicit drug use. We examined odds ratios for relevant characteristics in a multivariate logistic regression model to identify risk factors associated with opioid diversion.

Results

The screening question was presented to 1,176 patients, of whom 1,158 (98.5%) provided an answer. Of these, 541 (46.7%) responded 'yes' to ever having received an opioid prescription and were then asked to answer the opioid diversion questions. The sample was 61% male with a median age of 42 years (interquartile range: 35-49 years). The majority of patients (86%) were African American. Slightly more than half of the population (57%) reported an HIV acquisition risk factor of high-risk heterosexual, while 36% reported injection drug use and 22% reported men who have sex with men (MSM). Nearly all patients were taking antiretroviral therapy (93%) and 92% were virally suppressed. About one third of patients (34%) were never smokers, 23% were former smokers, and 42% were current smokers. Approximately 30% of patients had at least mild depressive symptoms on the PHQ-8 and about 20% had at least mild anxiety on the Generalized Anxiety Disorder scale. Illicit drug use was common among the sample: 57% had ever used marijuana, 51% had ever used cocaine, 38% had ever used non-medial opiates, 8% had ever used amphetamines, and 17% had ever used other illicit substances. Table 13 reports characteristics of the study sample.

The majority of patients who were presented with an opioid diversion question provided an answer, with only 13 patients (2.4%) leaving the question blank (5 skipped the direct question, 5 skipped the indirect question, and for the remaining 3 missing answers we were unable to determine whether the patient was presented with the direct or indirect questions). Supplementary Table 8 summarizes the responses to all opioid diversion questions during the data collection period.

Prevalence of opioid diversion

A total of 284 patients provided a response to the indirect question that asked patients to state whether their responses to the two questions presented was the same or different. About 70%, or 200 patients, stated that their response to both questions was the same and 84 (29.6%) responded that their responses to the two questions differed. Under the assumption that the expected probability of answering 'yes' to the mother's birthday being in February, April, or November is 23.5% (based on CDC and UN data for the number of births per month in the United States[8–10]), the calculated probability of opioid diversion under the indirect questioning technique was 11.5% (95% CI 6.4%-16.6%).

Overall, 244 patients directly answered whether they have ever diverted opioids, of whom 15 answered 'yes' for an overall probability of 6.1% (95% CI 3.5%-9.9%), indicating that the prevalence estimate nearly doubled under indirect questioning method.

Secondary analyses

In secondary analyses, the estimated prevalence of opioid diversion varied among sub-populations. Under the indirect questioning method, the prevalence estimate for women was 4.4% compared to 16.3% among men. African Americans had a smaller estimated prevalence (7.9%) compared to other races (25.5%). The most notable differences in prevalence occurred by history of illicit substance use: patients with a history of amphetamine use, cocaine use, and other illicit substances had prevalence estimates of 43.3%, 21.4%, and 28.5%, respectively, compared to prevalence estimates less than 7% for each of their respective counterparts. Stratified prevalence estimates using the direct questioning method were highest among patients with depression (12.2% vs. 4.9%), a history of amphetamine use (14.8% vs. 5.3%), and a history of other illicit drug use

(15.1% vs. 3.5%). Table 14 presents stratified prevalence estimates for subsets of the population under both the indirect and direct questioning methods.

In a multivariate adjusted logistic regression model for randomized response outcomes, ever-use of cocaine was strongly associated with opioid diversion, with an odds ratio of 16.3 (Table 15).

Discussion

Obtaining an estimate for the prevalence of opioid diversion is an important first step in combating the diversion problem in the United States. To measure progress, it is essential to understand the scope of the problem and to establish benchmarks for improvement. By consistently measuring the prevalence of opioid diversion, researchers and practitioners can assess the success of initiatives developed to reduce diversion and can gauge the need for additional targeted interventions. Applying an indirect questioning technique such as the crosswise method is a useful way to accurately determine changes in the prevalence of opioid diversion in a population.

We estimated an overall prevalence of opioid diversion of 6.1% using the direct questioning method and 11.5% using the indirect questioning method. Because of a paucity of literature on the prevalence of opioid diversion, we did not have a strong a priori hypothesis regarding the prevalence values; however, we did anticipate a meaningfully higher prevalence using the indirect questioning method. Our small, single-site study suggests that the crosswise method for indirect questioning does in fact provide a more accurate prevalence estimate for opioid diversion. We believe the estimate obtained via indirect questioning is a more accurate reflection of the true prevalence of opioid diversion as it is not subject to social desirability bias, which is a known drawback to self-reported measures of sensitive behaviors.

In our secondary analyses, we estimated the prevalence of opioid diversion among sub-populations; however, we did not have statistical power to determine significant differences between any of the strata. Similarly, we were not powered to detect statistically significant odds ratios in the multivariable logistic regression model. The odds ratios we present in our analysis should be considered explanatory; larger studies are needed to further assess characteristics associated with opioid diversion.

Our study sample was composed of PLWH from a single urban clinic who are all engaged in care, the majority of whom have good compliance with antiretroviral therapy. These patients are not representative of all PLWH, particularly those who are not engaged in care or those from non-urban settings. The prevalence of opioid diversion is likely highly variable across geographic regions; results from this one study should not be generalized to other populations. Nonetheless, the results from this study serve as a valuable example of an application of the crosswise method of indirect questioning to the estimation of opioid diversion in an urban HIV clinic. Additional studies are needed to determine the prevalence of opioid diversion in other populations.

The success of the crosswise method depends on the assumption that respondents understand the instructions provided; therefore, it is essential that the instructions be written in clear and simple language. We used prior examples from the literature to aid in the development of the written instructions[12]. Because patients did not have the option to provide a yes or no answer to the sensitive and non-sensitive questions, respondents who may not have understood the instructions were forced to consider the answer choices and could revisit the instructions to determine whether to choose the “same” or “different” answer choice. In future studies, more sophisticated pilot testing may be beneficial to ensure the study population fully understands the technique.

In addition to understanding the instructions, participants must also trust the method enough to provide an honest answer. Because we asked participants a sensitive question regarding an illegal behavior, a natural response is to lie for self-preservation. To minimize this, we chose to use the crosswise model, which does not have an obvious self-protective “no” answer. Alternative methods of indirect questioning[13,14] have the disadvantage of having a self-protective answer that participants may tend towards regardless of the truth. We chose to use the crosswise method for this aim in part due to its lack of a self-protective answer, which should help to increase the honesty of responses.

Although indirect questioning techniques elicit more honest responses than direct questioning, they are also associated with an increased variance of the prevalence estimate and consequently require a larger sample size to achieve adequate estimates. The sample size is dependent on the prevalence of both the sensitive and non-sensitive question, so we chose a non-sensitive question with low enough prevalence that the required sample size was feasible, but also high enough that the respondents would still feel their responses are protected.

In our study, the prevalence of the non-sensitive question was 23.5% according to prior literature from across the United States. However, if the prevalence of birthdays in our study sample differed from that of the general US population, the estimated prevalence of opioid diversion would be inaccurate. Supplementary Table 9 shows how the estimated prevalence of opioid diversion changes with various “true” prevalence measures for the non-sensitive question. For example, due to a programming error 198 patients in our study directly answered the non-sensitive question about their mother's birthday; 27.8% of these patients responded 'yes' (95% CI 21.7%-34.6%). Though this prevalence estimate is notably higher than the estimate used in our calculations, the confidence interval contains the value of 23.5% that was obtained from all live births in the United States. Therefore, we believe that the prevalence of the non-sensitive question for this analysis is accurate.

A final challenge associated with indirect questioning is that the resulting data are in aggregate rather than on an individual level. Indirect questioning techniques are useful for measuring the overall prevalence of a sensitive behavior in a population, and this has been the most often cited use of the technique. However, results from indirect questioning can also be used as both a predictor/covariate[15] and the response[16] in a regression model, and statistical packages have been developed in both R and Stata to appropriately fit these models. Though we were not powered to detect statistically significant characteristics associated with opioid diversion in this study, we conducted a secondary analysis in order to provide information that may be used to generate hypotheses for future research about factors that may be associated with opioid diversion among PLWH.

Despite these challenges, this study benefitted from several strengths. Most notably, we applied a unique methodology to estimate the prevalence of a behavior that is subject to strong social desirability bias, consequently rendering it difficult to study. The application of the crosswise method for indirect questioning allowed us to obtain an estimate for the prevalence of opioid diversion in our study population and provided a useful pilot study for future applications of this method to the study of opioid diversion. Another strength of this study is that our study sample came from an HIV clinic that is experienced in conducting research and is composed of patients who complete ACASI surveys as part of their standard of care. This setting provided us with patients who are accustomed to participating in research studies and also research assistants who were available to assist with the implementation of the survey question and clarify the instructions if needed. This was an ideal setting to test an uncommon questioning technique.

In this study, we found the estimated prevalence of opioid diversion using an indirect questioning method was nearly twice as high as the estimated prevalence obtained by directly asking the patients whether they have ever diverted opioids. The crosswise method for indirect questioning may be a useful technique for measuring the prevalence of opioid diversion while maintaining patients' anonymity and reducing social desirability bias. Further, we confirmed that opioid diversion is a serious public health concern among PLWH. Not only do PLWH receive more opioid than their uninfected counterparts, but the excess of opioid prescriptions appears to be associated with a high prevalence of diversion. Careful prescribing behavior and more stringent interventions are needed to mitigate opioid diversion.

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Table 13: Characteristics of study sample

N=1,158 patients who answered a screening question: "Has your doctor ever given you a prescription narcotic such as oxycontin, oxycodone, Percocet, fentanyl, tramadol, etc. to treat pain?" Patients who answered "Yes" to the screening question were included in the study sample.

	Screening: 'Yes' N=541	**Screening: 'No'** N=617	**Total** N=1,158
	N (%)	**N (%)**	**N (%)**
Age, median (IQR)	41 (35-49)	42 (35-49)	42 (35-49)
Sex			
Male	389 (63.0)	316 (58.4)	705 (60.9)
Female	228 (37.0)	225 (41.6)	453 (39.1)
Race/ethnicity			
African American	441 (81.5)	553 (89.6)	994 (85.8)
Other	100 (18.5)	64 (10.4)	164 (14.2)
HIV risk factor[1]			
High-risk heterosexual	301 (55.6)	358 (58.0)	659 (56.9)
MSM	131 (24.2)	121 (19.6)	252 (21.8)
IDU	190 (35.1)	231 (37.4)	421 (36.4)
Other	45 (8.3)	36 (5.8)	81 (7.0)
N/A	22 (4.1)	28 (4.5)	50 (4.3)
ART use			
Yes	504 (93.2)	574 (93.0)	1078 (93.1)
No	28 (5.2)	31 (5.0)	59 (5.1)
N/A	9 (1.7)	12 (1.9)	21 (1.8)
CD4			
<200	304 (56.2)	362 (58.7)	666 (57.5)
200-350	112 (20.7)	134 (21.7)	246 (21.2)
350-500	48 (8.9)	64 (10.4)	112 (9.7)
≥500	56 (10.4)	42 (6.8)	98 (8.5)
N/A	22 (4.1)	15 (2.4)	37 (3.2)
HIV viral suppression			
Yes	489 (90.4)	572 (92.7)	1061 (91.6)
No	47 (8.7)	39 (6.3)	86 (7.4)
N/A	6 (1.1)	6 (1.0)	12 (1.0)
Smoking status			
Never	167 (30.9)	232 (37.6)	399 (34.5)
Former	135 (25.0)	125 (20.3)	260 (22.5)
Current	231 (42.7)	253 (41.0)	484 (41.8)
N/A	8 (1.5)	7 (1.1)	15 (1.3)
PHQ-8			
None	128 (23.7)	266 (43.1)	394 (34.0)
Minimal	200 (37.0)	195 (31.6)	395 (34.1)
Mild	130 (24.0)	91 (14.7)	221 (19.1)

Moderate	43 (7.9)	29 (4.7)	72 (6.2)
Moderately severe	29 (5.4)	7 (1.1)	36 (3.1)
Severe	3 (0.6)	9 (1.5)	12 (1.0)
N/A	8 (1.5)	20 (3.2)	28 (2.4)
GAD			
None	293 (54.2)	378 (61.3)	671 (57.9)
Mild	63 (11.6)	47 (7.6)	110 (9.5)
Moderate	23 (4.3)	11 (1.8)	34 (2.9)
Severe	11 (2.0)	11 (1.8)	22 (1.9)
N/A	151 (27.9)	170 (27.6)	321 (27.7)
Audit			
<8	57 (10.5)	62 (10.0)	119 (10.3)
≥8	27 (5.0)	39 (6.3)	66 (5.7)
N/A	457 (84.5)	516 (83.6)	973 (84.0)
Cocaine			
Never	241 (44.5)	303 (49.1)	544 (47.0)
Ever	287 (53.0)	304 (49.3)	591 (51.0)
N/A	13 (2.4)	10 (1.6)	23 (2.0)
Amphetamines			
Never	417 (77.1)	517 (83.8)	934 (80.7)
Ever	55 (10.2)	36 (5.8)	91 (7.9)
N/A	69 (12.8)	64 (10.4)	133 (11.5)
Non-medical opiates			
Never	289 (53.4)	362 (58.7)	651 (56.2)
Ever	219 (40.5)	233 (36.1)	442 (38.2)
N/A	33 (6.1)	32 (5.2)	65 (5.6)
Marijuana			
Never	195 (36.0)	286 (46.4)	481 (41.5)
Ever	337 (62.3)	321 (52.0)	658 (56.8)
N/A	9 (1.7)	10 (1.6)	19 (1.6)
Other illicit drugs			
Never	381 (70.4)	485 (78.6)	866 (74.8)
Ever	111 (20.5)	85 (13.8)	196 (16.9)
N/A	49 (9.1)	47 (7.6)	96 (8.3)

[1]HIV risk factors are not mutually exclusive

Table 14: Stratified prevalence estimates for opioid diversion by hypothesized risk factors

Prevalence estimates for the indirect method are based on a probability of 0.235 for the non-sensitive question.

	Indirect Method N=284		Direct Method N=244	
	Sample size	Prevalence (95% CI)[1]	Sample size	Prevalence (95% CI)
Age				
<30	39	8.8 (0, 35.6)	29	3.4 (0.1, 17.8)
30 to <40	87	7.7 (0, 25.4)	75	8.0 (3.0, 16.6)
40 to <50	94	15.9 (0, 33.7)	86	8.1 (3.3, 16.1)
≥50	65	10.8 (0, 31.7)	54	1.9 (0, 9.9)
Sex				
Female	120	4.4 (0, 19.2)	103	5.8 (2.2, 12.2)
Male	165	16.3 (2.3, 29.7)	141	6.4 (3.0, 11.8)
Race/ethnicity				
African American	231	7.9 (0, 18.8)	200	5.5 (2.8, 9.6)
Other	54	25.5 (1.2, 49.8)	44	9.1 (2.5, 21.7)
HIV risk factor: high-risk heterosexual				
No	128	19.0 (3.6, 34.5)	105	8.6 (4.0, 15.6)
Yes	157	4.9 (0, 17.9)	139	4.3 (1.6, 9.2)
HIV risk factor: MSM				
No	217	7.8 (0, 19.1)	184	6.5 (3.4, 11.1)
Yes	68	22.3 (0.8, 43.7)	60	5.0 (1.0, 13.9)
HIV risk factor: IDU				
No	183	7.2 (0, 19.4)	163	4.3 (1.7, 8.6)
Yes	102	18.6 (1.3, 35.8)	81	9.9 (4.4, 18.5)
Smoking status				
Never	87	5.5 (0, 23.0)	76	3.9 (0.8, 11.1)
Ever	195	11.8 (0, 23.9)	165	7.3 (3.8, 12.4)
Depression				
None or minimal	175	12.8 (0, 25.6)	203	4.9 (2.4, 8.9)
Mild to severe	102	7.5 (0, 23.8)	41	12.2 (4.1, 26.2)
Anxiety				
None	158	11.8 (0, 25.2)	130	6.9 (3.2, 12.7)
Mild to severe	55	7.1 (0, 29.3)	39	7.7 (1.6, 20.9)
Marijuana				
Never	97	10.1 (0, 27.1)	90	4.4 (1.2, 11.0)
Ever	183	10.3 (0, 22.7)	151	6.6 (3.2, 11.8)
Amphetamines				
Never	220	6.3 (0, 17.3)	190	5.3 (2.6, 9.5)
Ever	28	43.3 (8.4, 78.1)	27	14.8 (4.2, 33.7)

Cocaine				
Never	125	0 (0, 0.1)	112	3.6 (1.0, 8.9)
Ever	152	21.4 (7.2, 35.7)	127	8.7 (4.4, 15.0)
Non-medical opiates				
Never	154	5.9 (0, 19.1)	130	3.8 (1.3, 8.7)
Ever	116	17.5 (1.3, 33.6)	100	9.0 (4.2, 16.4)
Other illicit drugs				
Never	202	7.0 (0, 18.6)	171	3.5 (1.3, 7.5)
Ever	57	28.5 (4.6, 52.3)	53	15.1 (6.7, 27.6)

[1]For estimated confidence intervals that contain zero, the lower confidence limit is listed as zero.

Table 15: Results from multivariate logistic regression models using crosswise technique

Odds ratios for ever having diverted an opioid prescription; N=284

	OR (95% CI)
Sex	
Female	Ref
Male	1.24 (0.04, 39.01)
HIV risk factor: high-risk heterosexual	
No	Ref
Yes	0.69 (0.06, 7.48)
HIV risk factor: MSM	
No	Ref
Yes	2.76 (0.27, 27.89)
HIV risk factor: IDU	
No	Ref
Yes	1.78 (0.08, 38.46)
Cocaine	
Never	Ref
Ever	16.29 (<0.01, 637,917.6)
Non-medical opiates	
Never	Ref
Ever	1.10 (0.13, 9.47)

Supplementary Table 8: Summary of responses to opioid diversion questions

Time period 1: October 24, 2016 through January 27, 2017
Time period 2: January 28, 2017 through February 14, 2017
Time period 3: February 15, 2017 through June 29, 2017

	N (% of non-N/A responses)			
	Time Period 1 N=470	**Time Period 2** N=86	**Time Period 3** N=620	**Total** N=1176
Screening				
Yes	200 (43.2)	37 (43.5)	304 (49.8)	541 (46.7)
No	263 (56.8)	48 (56.5)	306 (50.2)	617 (53.3)
Total	**463**	**85**	**610**	**1158**
N/A	*7*	*1*	*10*	*18*
Birthday				
Yes	55 (27.8)			55 (27.8)
No	143 (72.2)	--	--	143 (72.2)
Total	**198**			**198**
N/A	*272*			*272*
Direct				
Yes	10 (5.1)		5 (10.2)	15 (6.1)
No	185 (94.9)	--	44 (89.8)	229 (93.9)
Total	**195**		**49**	**244**
N/A	*275*		*571*	*846*
Indirect[1]				
Same		24 (75.0)	176 (69.8)	200 (70.4)
Different	--	8 (25.0)	76 (30.2)	84 (29.6)
Total		**32**	**252**	**284**
N/A		*6*	*368*	*374*

[1]Note: Between January 28, 2017 and February 14, 2017 everyone answered the indirect question, regardless of their response to the screening question (responses: 56 (74.7%) same, 19 (25.3%) different, 11 missing). The responses from patients who answered "No" to the screening question are re-coded as "N/A".

Supplementary Table 9 Estimated proportion of 'yes' responses to opioid diversion using Crosswise method of indirect questioning

P(birthday)=0.235*	P(birthday) = 0.242†	P(birthday)=0.278‡
0.115 (SE 0.051)	0.104 (SE 0.052)	0.040 (SE 0.061)

**Obtained from historical 1950 and 1955 CDC data and UN data for US births from 1969-2014*
†Calculated based on assumption of evenly distributed birthdays throughout the year
‡Based on responses from 198 patients who directly answered the question about their mother's birthday; 95% confidence interval for the measured proportion of birthdays in February, April, or November is 21.7-34.6%

Appendix: Sample size considerations

We calculated the sample size required to estimate the prevalence of opioid diversion in the JHHCC using indirect questioning by conservatively assuming a 25% probability of the non-sensitive question (CDC and UN data indicate a prevalence of 23.5%). The required sample size to detect a non-zero prevalence with 80% power using a 25% prevalent non-sensitive question and assuming a 15% true prevalence of opioid diversion is 218; therefore we aimed recruit 240 to ensure we can achieve the necessary power accounting for missing responses. Ulrich et al. explains the sample size calculation required for the crosswise method of indirect questioning[17] .

We calculated the sample size required for the direct questioning method assuming a reported prevalence of opioid diversion of 7%. Based on the same desired power (80%), Type I error (5%), and 10% non-response rate, we aimed to recruit 260 participants to directly answer whether they have ever diverted opioids. This would provide a sufficient sample size to detect a difference between the prevalence of opioid diversion as estimated through direct versus indirect questioning.

Discussion

Summary of findings

Using Medicaid prescription claims data from 14 states across the United States, we found an increased prevalence of prescription analgesic use among PLWH compared to individuals without HIV since the start of the 21st century. All analgesic use increased sharply between 2001 and 2009, with a similar rate of increase regardless of HIV status. When we restricted the study sample to patients with diabetes and weighted the population by the inverse probability of having an HIV diagnosis, differences in the prevalence of analgesic use diminished, suggesting that the increased analgesic use among PLWH is primarily explained by differences in demographic and clinical characteristics. Overall, we found that PLWH did not receive fewer analgesics compared to patients without HIV with similar clinical and demographic characteristics (and, presumably, similar levels of pain), which is contrary to early reports of an under-treatment of pain among PLWH compared to their HIV-uninfected counterparts[1–3], but consistent with recent literature suggesting an increase in opioid use among PLWH compared to individuals without HIV[4,5].

We found that progression to chronic opioid therapy (COT) among opioid-naïve individuals was relatively uncommon, with an overall incidence rate of approximately 9.6 per 1,000 person-years. PLWH had a significantly higher incidence of COT, with an incidence rate of 29.1 per 1,000 person-years. In an unadjusted Cox regression model, PLWH had three times the hazard for COT compared to individuals without HIV, but the increased hazard became non-significant when we restricted the sample to a homogeneous sample of patients with diabetes and adjusted for age, sex, state of residence, and relevant comorbidities.

A detailed analysis of the trends in opioid use is an important first step in understanding the opioid epidemic among a vulnerable population, such as PLWH. Following our analysis of trends in opioid and non-opioid use over time and the association between HIV status and the incidence of COT, we examined the incidence of high-risk opioid use among a clinical cohort of PLWH from clinics in three urban US cities. We identified 'high-risk' opioid use by observing prescribing patterns, which is a surrogate marker for true opioid misuse; however, prescribing patterns have been used in prior literature to identify high-risk opioid use and these patterns have been validated against clinical outcomes such as overdose and opioid addiction[6–16]. We examined four prescribing patterns: high daily dosage, overlapping prescriptions, multiple prescribers, and early refills.

In our sample of 1,794 incident opioid users living with HIV, approximately one third developed high-risk opioid use. The most common high-risk use behavior was multiple providers, with an incidence rate of 10.7 per 100 person-years. Early refills and overlapping prescriptions each had an incidence rate of approximately 9 per 100 person-years, and high daily dosage was least common with an incidence rate of approximately 6 per 100 person-years. Nearly half of the total cumulative incidence of high-risk use occurred within the first year after an opioid-naïve patient received an incident opioid prescription.

Consequences of inappropriate opioid receipt are wide-ranging and include both intentional and unintentional behaviors, such as overdose, addiction and dependence.

Adverse events from opioid misuse can also occur among patients who did not receive an opioid prescription from a medical provider, but rather who received opioids illicitly from a family member, friend, or stranger. In fact, the majority of abused painkillers were obtained illegally through opioid diversion[17]. Because of its harmful effects and limited research, opioid diversion is an important behavior to study.

We applied the crosswise method for indirect questioning[18] to estimate the prevalence of opioid diversion in the Johns Hopkins HIV Clinical Cohort. Among a sample of 284 PLWH, we estimated the prevalence of opioid diversion to be 11.5%, which was nearly twice as high as the prevalence we measured among 244 PLWH who directly answered whether they had ever diverted opioids (6.1%). We found that the indirect questioning method is an effective technique to apply to the study of opioid diversion, as patients tend to under-report this behavior. In a secondary analysis, we found that patients who had ever used cocaine were more likely to divert opioids; however, our small sample size precluded our ability to determine other factors that were significantly associated with opioid diversion.

Implications and public health significance

Prescription drug abuse has become a serious health problem in the United States in recent years[19–24]. The number of opioid prescriptions in circulation has increased dramatically[24], causing adverse effects such as opioid abuse, addiction, and overdose. Reducing the number of opioid prescriptions in circulation is an effective way to minimize opioid misuse; an excess of opioid prescriptions can lead to diversion and overdose. However, refraining from prescribing opioid medications also has consequences, including the persistence of pain symptoms. There must be a delicate balance between over-prescription of opioids and under-treatment of chronic pain, particularly among high-risk populations such as PLWH who are at increased risk for both chronic pain and opioid misuse.

Clearly elucidating the trends in opioid prescription patterns among PLWH and individuals without HIV was an important first step in studying the treatment of pain among PLWH. By using techniques such as weighting, restriction, and regression adjustment, we were able to compare PLWH to similar individuals without HIV to determine whether analgesic receipt and chronic opioid therapy differed by HIV status. Though differences in analgesic receipt by HIV status diminished after adjusting for clinical and demographic characteristics, which suggests similar treatment patterns by HIV status among patients with similar levels of pain, we did find a notably higher prevalence of analgesic use among PLWH in unadjusted trends. These results imply that PLWH have a greater need for analgesic prescriptions compared to individuals without HIV, emphasizing the importance of chronic pain management as a component of HIV treatment.

Further, the similar increase we observed in both opioid and non-opioid analgesic prescriptions indicates a lack of evidence for a switch from non-opioid therapy to opioid therapy. Though we did not hypothesize a switch from one type of analgesic treatment to another, prior literature that describes overall increases in opioid prescriptions might imply a reduction in non-opioid analgesic therapies as patients turn towards opioid pain treatment. However, we found an increase in all analgesic therapy, suggesting that pain is either becoming a more prevalent condition, or patients are being treated for pain more regularly. With the development of guidelines to encourage appropriate opioid prescribing, we would hope to see a larger increase in non-opioid therapies compared to opioid medication in the future.

The rise in opioid prescriptions is most concerning because it can lead to opioid misuse; it is important to study not only opioid prescribing but also high-risk opioid use. In our second study, we estimated the incidence of high-risk opioid use and described risk factors for high-risk opioid use using a large and comprehensive longitudinal clinical HIV cohort. We found that PLWH who receive opioid prescriptions often do so in patterns that are predictive of high-risk opioid use, with one third of incident opioid recipients meeting high-risk use criteria. This corresponds to a large proportion of all PLWH, as opioid use is common among PLWH. The results from our first two studies, in combination, confirm that PLWH are a particularly vulnerable population with respect to both opioid use and the potential for opioid misuse.

Opioid prescribing should always be accompanied by a clear discussion of the proper use of opioid medication and the risks associated with opioid therapy. These conversations may be especially helpful to patients who are at highest risk for misuse. We found that high-risk opioid use was particularly common among patients with a history of injection drug use, non-Hispanic whites, patients aged 35-45 years, and patients who had not achieved HIV suppression. While all patients should undergo counseling when initiating opioid therapy, patients with these characteristics may benefit from additional counseling and careful monitoring.

Our research on high-risk opioid use focused on PLWH. Nonetheless, some of our findings can apply not only to PLWH but to all high-risk populations and all patients whose opioid utilization behavior is tracked by prescription drug monitoring programs (PDMPs).

PDMPs help providers identify patients who receive opioids in patterns that are high-risk; however, they are often lacking in sensitivity and specificity and are consequently not often successful in identifying the most high-risk patients. We found correlation between the four high-risk use patterns we examined, though few patients met all criteria. Applying more sophisticated algorithms based on a combination of high-risk filling patterns could help improve the success of screening tools such as PDMPs.

There is a notable lack of research on one particular form of opioid misuse: diversion. The increasing number of opioid prescriptions in circulation across the United States makes opioid diversion a serious concern, particularly among PLWH. More opioid prescriptions are dispensed to PLWH compared to patients without HIV; having greater access to opioid medication increases the likelihood of having excess drugs available to divert. Diverted opioids mean that some victims of opioid overdose have not received a prescription directly and therefore cannot be identified by healthcare providers as being at-risk for opioid overdose. Understanding the burden of opioid diversion is essential to fully recognizing the impact of the opioid epidemic in the United States. Identifying risk factors for opioid diversion can help health practitioners and policy makers create targeted interventions to minimize diversion.

To our knowledge, the application of an indirect questioning technique to the study of opioid diversion has not been done previously. We used the crosswise method of indirect questioning to estimate the prevalence of opioid diversion in the Johns Hopkins HIV Clinical Cohort without the impact of social desirability bias and found a prevalence of diversion of nearly 12%. Though our study was conducted in a small and fairly homogeneous population of PLWH seeking care at one urban clinic in the mid-Atlantic region, the success of our study has implications for future research. We found that indirect questioning methods may be a useful way to study opioid diversion. Obtaining consistent measures of opioid diversion can be used to determine the impact of interventions such as the implementation of prescription drug monitoring programs or strict prescribing guidelines on the reducing the prevalence of opioid diversion.

Limitations and strengths

Defining opioid and non-opioid analgesics

This research was subject to several challenges and limitations. A first challenge relates to the identification of opioid and non-opioid analgesics. We used a list of NDCs that was compiled by researchers in collaboration with clinical experts to define the analgesics included in our study. However, all analgesics were identified using prescription claims records alone, without knowledge of their clinical indication. With regards to the non-opioid analgesics in particular, which included NSAIDs, anti-depressants, anticonvulsants, and muscle relaxants, the drugs are used for a variety of indications and are only occasionally used off-label to treat pain. In Chapter 2, it is possible that we attributed drugs to the treatment of pain when they were in fact being used for other indications. Also, some of the opioid analgesics included in both Chapters 2 and 3 could have been prescribed for the treatment of opioid addiction (i.e. buprenorphine); however, because all opioids are subject to misuse we chose a more inclusive definition for these analyses.

Time period of data

A second limitation of Chapters 2 and 3 is that the data analyzed were collected nearly a decade ago. The opioid epidemic has become a serious public health concern in recent years, leading to secular changes that might impact our results if our studies were repeated with more recent data. Nonetheless, understanding historic trends is valuable in its own right, as it puts recent trends into context and allows us to determine changes in the prevalence of analgesic prescriptions, the incidence of chronic opioid therapy, and the incidence of high-risk opioid use.

Despite the timeframe of the data, we chose to use historic data for the Chapter 2 analysis because of the immense value that the data provided. Specifically, Medicaid claims files provide information on a large subset of PLWH since Medicaid covers nearly 40% of insured PLWH[27]. Claims files served as the best data source for the analysis of trends in analgesic prescribing because they provide data on all prescriptions dispensed, regardless of the prescribing physician. Having existing access to these Medicaid files provided a significant advantage that allowed for a meaningful analysis.

The data analyzed for Chapter 3 were collected between 2006-2010. As with Chapter 2, we chose to analyze these historic data because of the value they provided. The dataset for Chapter 3 was composed of both clinical cohort data from the HIV Research Network (HIVRN) and also comprehensive Medicaid pharmaceutical claims. Performing an individual-level linkage between the HIVRN and Medicaid is resource-intensive, and having such a rich data source available is rare. Therefore, despite the time period, these data provided us with a unique opportunity to analyze the incidence high-risk opioid use prescribing patterns and also examining demographic, clinical, and behavioral characteristics associated with the high-risk opioid use.

Challenges with primary data collection

We collected data for Chapter 4 by designing survey questions to add to an existing patient-reported outcomes survey. As is often the case with primary data collection, particularly when the questions involve a novel questioning technique, we faced challenges in the development and implementation of these questions. We performed a basic pilot test among a convenience sample of patients to ensure they understood the indirect questioning method and instructions. Nonetheless, most patients are unfamiliar with the technique and may have been confused by the questions.

Additionally, we faced challenges in programming the question. In the first iteration of the indirect question, the two parts to the question (i.e. the non-sensitive question asking patients whether the patient's mother's birthday was in February, April, or November, and the sensitive question asking patients if they have ever diverted opioids) were programmed as separate questions. As such, we inadvertently collected data on patient's mother's birth month and direct responses to opioid diversion only. We were able to use the responses to the birthday question to validate our estimate for the prevalence of the non-sensitive question, but required additional time to complete data collection for the indirect question. Because the entire data collection period occurred over approximately a seven-month period, we do not expect that there were temporal trends that impacted our results.

Innovation and contribution to the literature

Though prior studies have described trends in opioid utilization and high-risk opioid use, this research contributed to the literature in several important respects. First, a unique feature of this research is that it focused exclusively on people living with HIV.

Much of the prior research on trends in opioid use has examined the entire US population, cancer patients, or patients with non-cancer chronic disease[6,9,28–32]. Little research has focused on analyzing trends among PLWH specifically.

Another strength of this research is that we used longitudinal data, following cohorts of individuals over time both in Chapter 2 (using a closed cohort of Medicaid-enrolled individuals) and in Chapter 3 (using a longitudinal clinical cohort). This allowed us to identify incident chronic opioid therapy and incident high-risk opioid use among opioid-naïve individuals.

Additionally, the research in Chapter 3 benefited from the innovative use of two distinct but complementary data sources: 1) Medicaid claims data, which provided comprehensive pharmaceutical information that is difficult to obtain, particularly in such a large quantity, using clinical or observational cohorts and 2) HIVRN clinical cohort data that provided additional information regarding socio-demographic, behavioral, and clinical information that we were unable to obtain from Medicaid databases. The ability to link records from the clinical cohorts to Medicaid allowed for a sophisticated and informative analysis that would not have been possible with either of the two data sources alone.

Finally, the use of an indirect questioning method to estimate the prevalence of opioid diversion is novel to this field of study. Such techniques have been applied to illicit drug use in other populations, but to our knowledge this approach has not been used to study prescription opioid diversion among PLWH. The simultaneous application of the crosswise method of indirect questioning and the use of direct questioning allowed us to compare the prevalence of opioid diversion using two distinct methods and helped us to quantify the under-report of opioid diversion using direct questioning methods.

Future directions

Update analyses using data from recent years

This research could be strengthened by future studies that examine more recent trends in opioid and non-opioid analgesic utilization by HIV status. In Chapter 2, we analyzed prescription claims through 2009. Since then, changes in HIV treatment and acquisition as well as changes in opioid prescribing recommendations may have altered the associations we found in our analysis, either regarding the prevalence of opioid and non-opioid analgesics or in the incidence of progression to COT by HIV status. Extending the analysis we conducted in Chapter 2 to include analgesic prescription utilization since 2009 would allow us to assess the impact of recent opioid prescribing guidelines and determine whether changes in opioid prescribing practices, including the recent stabilization and even decrease in some populations in the number opioid prescriptions across the United States[24], differs by HIV status.

Similarly, further research is warranted to describe recent trends in the incidence of high-risk opioid use among PLWH. Widespread adoption of prescription drug monitoring programs by nearly all US states has impacted opioid prescribing behaviors, albeit to varying extents across states[33], and consequently could impact the outcomes analyzed in Chapter 3. Because the rate of high-risk opioid use was high in our study population, there is an opportunity for significant improvement in opioid prescribing patterns among PLWH. It is currently not known whether, and to what extent, the recent focus on restricting opioid availability and minimizing inappropriate prescribing has impacted high-risk opioid use among PLWH. Analyzing trends in high-risk opioid use since 2010 would provide evidence for the impact of recent prescribing guidelines and interventions on high-risk opioid use among high-risk populations such as PLWH.

Validate and compare each high-risk prescribing behavior

In Chapter 3, we analyzed four distinct opioid prescribing patterns as a surrogate marker for high-risk opioid use. All four of these patterns have been used in research settings previously to describe high-risk use behaviors[6–16], but to our knowledge they have not been directly compared to one another. To help determine the best method to identify high-risk opioid use through the analysis of prescription claims, it would be beneficial to conduct an analysis specifically comparing the four patterns, or various combinations of the patterns, to determine their association with clinical outcomes including addiction, dependence, overdose, diversion, and mortality. For example, it might be true that patients who meet criteria for two specific patterns are at highest risk for adverse outcomes. Future research that aims to identify the optimal application of prescription claims to detect high-risk prescribing could provide guidance on identifying which patients are truly at highest risk for adverse outcomes. The results could be applied to existing prescription drug monitoring programs, improving their algorithms for detecting high-risk patients. Patients filling prescriptions in patterns that are most hazardous should be flagged, allowing providers the opportunity to reconsider prescribing the opioid or to provide additional counseling on the potential harms of the medication.

Continue research on opioid diversion

The study of opioid diversion is still nascent. Though we know that the majority of overdoses occur from drugs that were obtained illicitly[17], we do not have a clear understanding of the extent to which opioid diversion occurs. In Chapter 4, were conducted a small study to determine whether the crosswise method of indirect questioning might be a feasible technique to study the prevalence of opioid diversion. We found that the prevalence of opioid diversion was nearly twice as high in our study population compared to using a direct questioning method, although the prevalence was still lower than the reported prevalence among European patients in opioid substitution treatment programs, which was up to 34%[34,35]. The field of research into opioid diversion would benefit from larger studies in more diverse study populations to estimate the prevalence of opioid diversion more broadly. Applying the indirect questioning technique on a larger scale would also allow for the estimation of stratified prevalence estimates and the analysis of risk factors associated with opioid diversion. Identifying sets of risk factors may allow for targeted intervention to reduce opioid diversion.

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opioid substitution treatment in Sweden : Prevalence estimates and risk factors. *Int J Drug Policy*. 2015;26(2):183-190. doi:10.1016/j.drugpo.2014.10.003.

Curriculum Vitae

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EDUCATION

PhD	Johns Hopkins Bloomberg School of Public Health Baltimore, MD Concentration*:* General Epidemiology and Methodology Certificate in Pharmacoepidemiology and Drug Safety
MPH	University of Louisville School of Public Health and Information Sciences Louisville, KY Degree awarded: May 2012 Concentration*:* Biostatistics
BA	Brandeis University Waltham, MA Degree awarded: May 2009, Magna Cum Laude Majors: Health: Science, Society and Policy; Psychology Minor: Economics

PROFESSIONAL EXPERIENCE

October 2015 – July 2016	CVS Health; remote Consulting Researcher
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July 2012 – February 2013	Edumedics, LLC; Louisville, KY Data Analyst
June 2010 – July 2012	Norton Leatherman Spine Center; Louisville, KY Clinical Research Assistant

February 2009 – June 2010 HealthMETRICS Partners, Inc.; Lexington, MA
Analyst

October 2009 – June 2010 Sterling Planning Alliance; Boston, MA
Health Planner

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Undergraduate Research Assistant

TEACHING EXPERIENCE

2016 Advanced Methods for the Design and Analysis of Cohort Studies
Teaching Assistant

2015 Spatial Analysis and GIS II
Teaching Assistant

2014 Epidemiologic Methods II
Teaching Assistant

ACTIVITIES AND VOLUNTEER EXPERIENCE

2016-2017 Epidemiology Student Organizations; Baltimore, MD
President

2014-2015 General Epidemiology and Methodology Journal Club; Baltimore, MD
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2011-2012 School of Public Health Student Government; Louisville, KY
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2011-2012 SPHIS SGA Peer Mentoring Program; Louisville KY
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2010-2012 Kaplan Test Prep; Louisville, KY
GRE Teacher and Tutor

2006-2009 Pepperberg Lab; Waltham, MA
Lab Assistant

PROFESSIONAL MEMBERSHIPS

2015-2017 Society for Epidemiologic Research (SER)

2016-2017 International AIDS Society (IAS)

2016-2017 International Society for Pharmacoepidemiology (IPSE)

EDITORIAL EXPERIENCE

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Peer Reviewer

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HONORS AND AWARDS

2015-2017 HIV T32 Pre-doctoral Fellowship

2012 North American Spine Society, Value Abstract Award

2012 Delta Omega Honorary Society in Public Health

2012 Graduate Dean's Citation, University of Louisville SPHIS

2012 HRSA Public Health Scholarship

2009 Magna Cum Laude, Brandeis University

2008 Psi Chi: The International Honor Society in Psychology

2005-2009 Alumni and Friends Scholarship, Brandeis University

2009-2009 Bank of America Joe Martin Scholarship

2005-2009 Greater Worcester Community Foundation Tilton Memorial Scholarship

PUBLICATIONS

1. **Canan CE,** Polinski JM, Alexander GC, Kowal MK, Brennan TA, Shrank WH. Automatable algorithms to identify nonmedical opioid use using electronic data: a systematic review. *Journal of the American Medical Informatics Association:* in press.

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PRESENTATIONS

1. **Canan CE**, Chander G, Alexander, GC, Monroe A, Gebo K, Moore RD, Agwu A, Lau B. High-risk prescription opioid use among people with HIV. *Society of General Internal Medicine Annual Meeting, Washington D.C, April 2017.* [Presentation]

2. **Canan CE,** Lesko C, Lau B. Instrumental Variables Analyses are Subject to Selection Bias. *Epidemiology Congress of the Americas, Miami, Florida, June 2016.* [Poster]

3. **Canan CE**, Lau B, McCaul ME, Moore RD, Chander G. Effect of Alcohol on All-Cause and Liver-Related Mortality among Individuals with HIV. *Conference on Retroviruses and Opportunistic Infections, Boston, Massachusetts, February 2016.* [Poster]

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5. **Canan CE**, Myers J, Gall S. Optimal Week of Gestation in which to Administer the Tdap Vaccine during Pregnancy. *Research!Louisville, Louisville, Kentucky, October 2011.* [Poster]